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(54) **Title:** METABOLICALLY STABLE SIGMA RECEPTOR LIGANDS

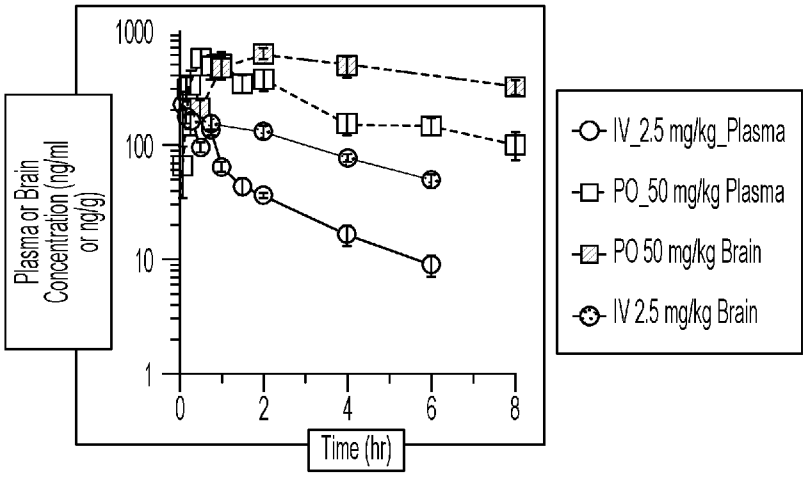

FIG. 1A

(57) **Abstract:** Described herein are new metabolically stable sigma receptor small molecule antagonists of any of the formulae herein, including for example, Formula (I), Formula (II), and Formula (III). The compounds are useful for treating and/or preventing diseases and disorders (e.g., pain, neurodegenerative disorders (e.g., Alzheimer disease, Parkinson's disease), substance addiction, cancer, depression, schizophrenia, anxiety, stroke, obsessive compulsive disorder, or multiple sclerosis).

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METABOLICALLY STABLE SIGMA RECEPTOR LIGANDS

RELATED APPLICATIONS

[01] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application, U.S.S.N. 63/434,848, filed December 22, 2022, which is incorporated herein by reference.

GOVERNMENT SUPPORT

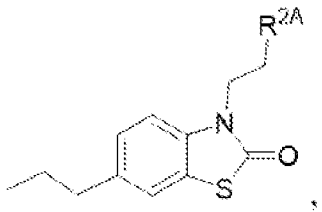
[02] This invention was made with government support under W81XWH-17-1-0557 awarded by the U.S. Army Medical Research Acquisition Activity. The government has certain rights in the invention.

BACKGROUND

[03] Sigma receptors are a well-defined unique class of receptors and are highly expressed in the central nervous system and also widely distributed in peripheral organs and tissues that serve as targets for psychostimulant drugs (Matsumoto, R. *et al. Expert Rev. Clin. Pharmacol.* 2009; 2: 351–358). Many commonly abused drugs interact with sigma receptors including, for example, cocaine, methamphetamine, and even some opioids (Matsumoto, R. *et al. Expert Rev. Clin. Pharmacol.* 2009; 2: 351–358). In addition to sigma receptors being associated with psychostimulant drugs, these receptors are also associated with various other diseases and disorders including depression, anxiety, schizophrenia, psychosis, pain, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, retinal diseases, and stroke (Hayashi, T. *et al. CNS Drugs* 2004; 18, 269-284; Hayashi, T. *et al. Expert Opin. Ther. Targets* 2011; 15, 557-577; Kaushal, N. *et al. Eur. Neuropsychopharmacol.* 2013; 23, 960–971). Additionally, sigma receptors play a role in cancer (Aydar, R. *et al. Cancer Res.* 2004; 64, 5029-5035; Van Waarde, A. *et al. Curr. Pharm. Des.* 2010; 16, 3519–3537), cardiovascular diseases (Monassier, L. *et al. Fundam. Clin. Pharmacol.* 2002; 16, 1–8), inflammatory and autoimmune diseases (Bourrie, B. *et al. Expert Opin. Investig. Drugs* 2004; 5, 1158–1163; Su, T. P. *et al. Science*, 1988; 240, 219-221; Wolfe, S. A. *et al.* J. *Pharmacol. Exp. Ther.* 1988; 247, 1114–1119).

SUMMARY OF THE INVENTION

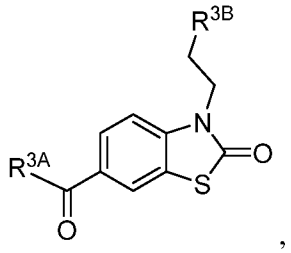
[04] Described herein are new dual sigma receptor small molecule antagonists. These compounds present suitable metabolic stability and bioavailability. In one aspect, provided herein are compounds of Formula (I):



(I)

or pharmaceutically acceptable salt thereof, wherein R^{2A} is as defined herein.

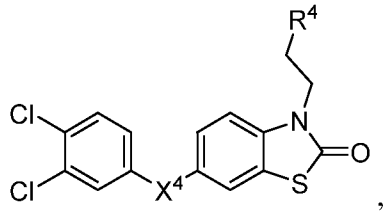
[05] In a further aspect, provide herein are compounds of Formula (II):



(II)

or pharmaceutically acceptable salt thereof, wherein R^{3A} and R^{3B} are as defined herein.

[05] In another aspect, provided herein are compounds of Formula (III):



(III)

or pharmaceutically acceptable salt thereof, wherein R^4 and X^4 are as defined herein.

[06] In another aspect, provided herein are compositions comprising a compound provided herein (*e.g.*, a compound of Formula (I), (II), or (III)), or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient

[07] In an additional aspect, the present disclosure provides methods of treating or preventing substance intake by a subject comprising administering to the subject a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Formula (I), (II), or (III)), or pharmaceutically acceptable salt thereof, or a composition provided herein (*e.g.*, a composition comprising a compound of Formula (I), (II), or (III)).

[08] In another aspect, provided herein are methods of treating or preventing a substance use disorder in a subject comprising administering to the subject a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Formula (I), (II), or (III)), or pharmaceutically acceptable salt thereof, or a composition provided herein (*e.g.*, a composition comprising a compound of Formula (I), (II), or (III)).

[09] In one aspect, the present disclosure provides methods of treating the symptoms of substance use disorder in a subject comprising administering to the subject a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Formula (I), (II), or (III)), or pharmaceutically acceptable salt thereof, or a composition provided herein (*e.g.*, a composition comprising a compound of Formula (I), (II), or (III)).

[010] In an additional aspect, the present disclosure provides methods of treating or preventing substance addiction by a subject comprising administering to the subject a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Formula (I), (II), or (III)), or pharmaceutically acceptable salt thereof, or a composition provided herein (*e.g.*, a composition comprising a compound of Formula (I), (II), or (III)).

[011] In another aspects, provided herein are methods of treating the symptoms of substance addiction by a subject comprising administering to the subject a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Formula (I), (II), or (III)), or pharmaceutically acceptable salt thereof, or a composition provided herein (*e.g.*, a composition comprising a compound of Formula (I), (II), or (III)).

[012] In one aspect, the present disclosure provides methods of treating or preventing neurotoxic effects resulting from substance use disorder, substance addiction, and/or substance intake in a subject comprising administering to the subject a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Formula (I), (II), or (III)), or pharmaceutically acceptable salt thereof, or a composition provided herein (*e.g.*, a composition comprising a compound of Formula (I), (II), or (III)).

[013] In a further aspect, provided herein are methods of treating or preventing a disease or disorder associated with one or more sigma receptors comprising administering to a subject a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Formula (I), (II), or (III)), or pharmaceutically acceptable salt thereof, or a composition provided herein (*e.g.*, a composition comprising a compound of Formula (I), (II), or (III)). In some embodiments,

the disease or disorder is a neurological disease, a proliferative disease, a painful condition, or a psychiatric disorder. In some embodiments, the disease or disorder is pain, a neurodegenerative disorder (*e.g.*, Alzheimer's disease, Parkinson's disease), substance addiction, cancer, depression, schizophrenia, anxiety, stroke, obsessive compulsive disorder, or multiple sclerosis.

[014] In one aspect, the present disclosure provides a kit comprising: a compound provided herein (*e.g.*, a compound of Formula (I), (II), or (III)), or pharmaceutically acceptable salt thereof, or a composition provided herein (*e.g.*, a composition comprising a compound of Formula (I), (II), or (III)); and instructions for administering the compound, or pharmaceutically acceptable salt thereof, or composition to a subject.

[015] Additional aspects of any of the above methods are those wherein the subject is in need of such treatment, and those wherein the subject is identified as in need of such treatment.

[016] The details of certain embodiments of the disclosure are set forth in the Detailed Description of Certain Embodiments, as described below. Other features, objects, and advantages of the disclosure will be apparent from the Definitions, Figures, Examples, and Claims. It should be understood that the aspects described herein are not limited to specific embodiments, methods, apparati, or configurations, and as such can, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only and, unless specifically defined herein, is not intended to be limiting.

DEFINITIONS

[017] For convenience, certain terms employed herein, in the specification, examples and appended claims are collected herein.

[018] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999;Michael B. Smith, *March's Advanced Organic Chemistry*, 7th Edition, John Wiley & Sons, Inc., New York, 2013; Richard C. Larock, *Comprehensive Organic Transformations*, John Wiley & Sons, Inc., New

York, 2018; and Carruthers, Some Modern Methods of Organic Synthesis, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[019] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various stereoisomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, Tetrahedron 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); and Wilen, S.H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The invention additionally encompasses compounds as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[020] The compounds herein may also contain linkages (e.g., carbon-carbon bonds) wherein bond rotation is restricted about that particular linkage, e.g., restriction resulting from the presence of a ring or double bond. Accordingly, all cis/trans and E/Z isomers are expressly included in the present disclosure. The compounds herein may also be represented in multiple tautomeric forms; in such instances, the present disclosure expressly includes all tautomeric forms of the compounds and oligonucleotides described herein, even though only a single tautomeric form may be represented. All such isomeric forms of such compounds herein are expressly included in the present disclosure. The term "isomers" is intended to include diastereoisomers, enantiomers, regioisomers, structural isomers, rotational isomers, tautomers, and the like. For compounds that contain one or more stereogenic centers, e.g., chiral compounds, the methods of the present disclosure may be carried out with an enantiomerically enriched compound, a racemate, or a mixture of diastereomers. All isomers of compounds delineated herein are expressly included in the present disclosure.

[021] The term "alkyl" refers to a radical of a straight-chain or branched saturated hydrocarbon group having from 1 to 20 carbon atoms ("C_{1-20} alkyl"). In some embodiments, an alkyl group

has 1 to 12 carbon atoms ("C_{1-12} alkyl"). In some embodiments, an alkyl group has 1 to 10 carbon atoms ("C_{1-10} alkyl"). In some embodiments, an alkyl group has 1 to 9 carbon atoms ("C_{1-9} alkyl"). In some embodiments, an alkyl group has 1 to 8 carbon atoms ("C_{1-8} alkyl"). In some embodiments, an alkyl group has 1 to 7 carbon atoms ("C_{1-7} alkyl"). In some embodiments, an alkyl group has 1 to 6 carbon atoms ("C_{1-6} alkyl"). In some embodiments, an alkyl group has 1 to 5 carbon atoms ("C_{1-5} alkyl"). In some embodiments, an alkyl group has 1 to 4 carbon atoms ("C_{1-4} alkyl"). In some embodiments, an alkyl group has 1 to 3 carbon atoms ("C_{1-3} alkyl"). In some embodiments, an alkyl group has 1 to 2 carbon atoms ("C_{1-2} alkyl"). In some embodiments, an alkyl group has 1 carbon atom ("C_1 alkyl"). In some embodiments, an alkyl group has 2 to 6 carbon atoms ("C_{2-6} alkyl"). Examples of C_{1-6} alkyl groups include methyl (C_1), ethyl (C_2), propyl (C_3) (*e.g.*, *n*-propyl, isopropyl), butyl (C_4) (*e.g.*, *n*-butyl, *tert*-butyl, *sec*-butyl, isobutyl), pentyl (C_5) (*e.g.*, *n*-pentyl, 3-pentanyl, amyl, neopentyl, 3-methyl-2-butanyl, *tert*-amyl), and hexyl (C_6) (*e.g.*, *n*-hexyl). Additional examples of alkyl groups include *n*-heptyl (C_7), *n*-octyl (C_8), *n*-dodecyl (C_{12}), and the like. Unless otherwise specified, each instance of an alkyl group is independently unsubstituted (an "unsubstituted alkyl") or substituted (a "substituted alkyl") with one or more substituents (*e.g.*, halogen, such as F). In certain embodiments, the alkyl group is an unsubstituted C_{1-12} alkyl (such as unsubstituted C_{1-6} alkyl, *e.g.*, $-CH_3$ (Me), unsubstituted ethyl (Et), unsubstituted propyl (Pr, *e.g.*, unsubstituted n-propyl (n-Pr), unsubstituted isopropyl (*i*-Pr)), unsubstituted butyl (Bu, *e.g.*, unsubstituted *n*-butyl (*n*-Bu), unsubstituted *tert*-butyl (*tert*-Bu or *t*-Bu), unsubstituted *sec*-butyl (*sec*-Bu or *s*-Bu), unsubstituted isobutyl (*i*-Bu)). In certain embodiments, the alkyl group is a substituted C_{1-12} alkyl (such as substituted C_{1-6} alkyl, *e.g.*, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, or benzyl (Bn)).

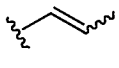
[022] The term "haloalkyl" is a substituted alkyl group, wherein one or more of the hydrogen atoms are independently replaced by a halogen, *e.g.*, fluoro, bromo, chloro, or iodo. "Perhaloalkyl" is a subset of haloalkyl, and refers to an alkyl group wherein all of the hydrogen atoms are independently replaced by a halogen, *e.g.*, fluoro, bromo, chloro, or iodo. In some embodiments, the haloalkyl moiety has 1 to 20 carbon atoms ("C_{1-20} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 10 carbon atoms ("C_{1-10} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 9 carbon atoms ("C_{1-9} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 8 carbon atoms ("C_{1-8} haloalkyl"). In some

embodiments, the haloalkyl moiety has 1 to 7 carbon atoms ("C_{1-7} haloalkyl").In some embodiments, the haloalkyl moiety has 1 to 6 carbon atoms ("C_{1-6} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 5 carbon atoms ("C_{1-5} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 4 carbon atoms ("C_{1-4} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 3 carbon atoms ("C_{1-3} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 2 carbon atoms ("C_{1-2} haloalkyl"). In some embodiments, all of the haloalkyl hydrogen atoms are independently replaced with fluoro to provide a "perfluoroalkyl" group. In some embodiments, all of the haloalkyl hydrogen atoms are independently replaced with chloro to provide a "perchloroalkyl" group. Examples of haloalkyl groups include $-CHF_2$, $-CH_2F$, $-CF_3$, $-CH_2CF_3$, $-CF_2CF_3$, $-CF_2CF_2CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, and the like.

[023] The term "heteroalkyl" refers to an alkyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*e.g.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 20 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-20} alkyl"). In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 12 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-12} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 11 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-11} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 10 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-10} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 9 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-9} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-8} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 7 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-7} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 6 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-6} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 5 carbon atoms and 1 or 2 heteroatoms within the parent chain ("heteroC_{1-5} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and

1or 2 heteroatoms within the parent chain ("heteroC_{1-4} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom within the parent chain ("heteroC_{1-3} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom within the parent chain ("heteroC_{1-2} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom ("heteroC_1 alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 2 to 6 carbon atoms and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-6} alkyl"). Unless otherwise specified, each instance of a heteroalkyl group is independently unsubstituted (an "unsubstituted heteroalkyl") or substituted (a "substituted heteroalkyl") with one or more substituents. In certain embodiments, the heteroalkyl group is an unsubstituted heteroC_{1-12} alkyl. In certain embodiments, the heteroalkyl group is a substituted heteroC_{1-12} alkyl.

[024] The term "alkenyl" refers to a radical of a straight-chain or branched hydrocarbon group having from 1 to 20 carbon atoms and one or more carbon-carbon double bonds (*e.g.*, 1, 2, 3, or 4 double bonds). In some embodiments, an alkenyl group has 1 to 20 carbon atoms ("C_{1-20} alkenyl"). In some embodiments, an alkenyl group has 1 to 12 carbon atoms ("C_{1-12} alkenyl"). In some embodiments, an alkenyl group has 1 to 11 carbon atoms ("C_{1-11} alkenyl"). In some embodiments, an alkenyl group has 1 to 10 carbon atoms ("C_{1-10} alkenyl"). In some embodiments, an alkenyl group has 1 to 9 carbon atoms ("C_{1-9} alkenyl"). In some embodiments, an alkenyl group has 1 to 8 carbon atoms ("C_{1-8} alkenyl"). In some embodiments, an alkenyl group has 1 to 7 carbon atoms ("C_{1-7} alkenyl"). In some embodiments, an alkenyl group has 1 to 6 carbon atoms ("C_{1-6} alkenyl"). In some embodiments, an alkenyl group has 1 to 5 carbon atoms ("C_{1-5} alkenyl"). In some embodiments, an alkenyl group has 1 to 4 carbon atoms ("C_{1-4} alkenyl"). In some embodiments, an alkenyl group has 1 to 3 carbon atoms ("C_{1-3} alkenyl"). In some embodiments, an alkenyl group has 1 to 2 carbon atoms ("C_{1-2} alkenyl"). In some embodiments, an alkenyl group has 1 carbon atom ("C_1 alkenyl"). The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of C_{1-4} alkenyl groups include methylidenyl (C_1), ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), and the like. Examples of C_{1-6} alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. Unless otherwise specified, each instance of an

alkenyl group is independently unsubstituted (an "unsubstituted alkenyl") or substituted (a "substituted alkenyl") with one or more substituents. In certain embodiments, the alkenyl group is an unsubstituted C_{1-20} alkenyl. In certain embodiments, the alkenyl group is a substituted C_{1-20} alkenyl. In an alkenyl group, a C=C double bond for which the stereochemistry is not specified (*e.g.*, $-CH=CHCH_3$ or ) may be in the (*E*)- or (*Z*)-configuration.

[025] The term "heteroalkenyl" refers to an alkenyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*e.g.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkenyl group refers to a group having from 1 to 20 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{1-20} alkenyl"). In certain embodiments, a heteroalkenyl group refers to a group having from 1 to 12 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{1-12} alkenyl"). In certain embodiments, a heteroalkenyl group refers to a group having from 1 to 11 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{1-11} alkenyl"). In certain embodiments, a heteroalkenyl group refers to a group having from 1 to 10 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{1-10} alkenyl"). In some embodiments, a heteroalkenyl group has 1 to 9 carbon atoms at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{1-9} alkenyl"). In some embodiments, a heteroalkenyl group has 1 to 8 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{1-8} alkenyl"). In some embodiments, a heteroalkenyl group has 1 to 7 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{1-7} alkenyl"). In some embodiments, a heteroalkenyl group has 1to 6 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{1-6} alkenyl"). In some embodiments, a heteroalkenyl group has 1 to 5 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{1-5} alkenyl"). In some embodiments, a heteroalkenyl group has 1 to 4 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{1-4} alkenyl"). In some embodiments, a heteroalkenyl group has 1 to 3 carbon atoms, at least one double bond, and 1 heteroatom within the parent chain ("heteroC_{1-3} alkenyl"). In some embodiments, a heteroalkenyl group has 1 to 2 carbon atoms, at least one double bond, and 1 heteroatom within the parent chain ("heteroC_{1-2} alkenyl"). In some embodiments, a

heteroalkenyl group has 1 to 6 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{1-6} alkenyl"). Unless otherwise specified, each instance of a heteroalkenyl group is independently unsubstituted (an "unsubstituted heteroalkenyl") or substituted (a "substituted heteroalkenyl") with one or more substituents. In certain embodiments, the heteroalkenyl group is an unsubstituted heteroC_{1-20} alkenyl. In certain embodiments, the heteroalkenyl group is a substituted heteroC_{1-20} alkenyl.

[026] The term "alkynyl" refers to a radical of a straight-chain or branched hydrocarbon group having from 1 to 20 carbon atoms and one or more carbon-carbon triple bonds (*e.g.*, 1, 2, 3, or 4 triple bonds) ("C_{1-20} alkynyl"). In some embodiments, an alkynyl group has 1 to 10 carbon atoms ("C_{1-10} alkynyl"). In some embodiments, an alkynyl group has 1 to 9 carbon atoms ("C_{1-9} alkynyl"). In some embodiments, an alkynyl group has 1 to 8 carbon atoms ("C_{1-8} alkynyl"). In some embodiments, an alkynyl group has 1 to 7 carbon atoms ("C_{1-7} alkynyl"). In some embodiments, an alkynyl group has 1 to 6 carbon atoms ("C_{1-6} alkynyl"). In some embodiments, an alkynyl group has 1 to 5 carbon atoms ("C_{1-5} alkynyl"). In some embodiments, an alkynyl group has 1 to 4 carbon atoms ("C_{1-4} alkynyl"). In some embodiments, an alkynyl group has 1 to 3 carbon atoms ("C_{1-3} alkynyl"). In some embodiments, an alkynyl group has 1 to 2 carbon atoms ("C_{1-2} alkynyl"). In some embodiments, an alkynyl group has 1 carbon atom ("C_1 alkynyl"). The one or more carbon-carbon triple bonds can be internal (such as in 2-butynyl) or terminal (such as in 1-butynyl). Examples of C_{1-4} alkynyl groups include, without limitation, methylidynyl (C_1), ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), and the like. Examples of C_{1-6} alkenyl groups include the aforementioned C_{2-4} alkynyl groups as well as pentynyl (C_5), hexynyl (C_6), and the like. Additional examples of alkynyl include heptynyl (C_7), octynyl (C_8), and the like. Unless otherwise specified, each instance of an alkynyl group is independently unsubstituted (an "unsubstituted alkynyl") or substituted (a "substituted alkynyl") with one or more substituents. In certain embodiments, the alkynyl group is an unsubstituted C_{1-20} alkynyl. In certain embodiments, the alkynyl group is a substituted C_{1-20} alkynyl.

[027] The term "heteroalkynyl" refers to an alkynyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*e.g.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkynyl group refers to a group having from 1

to 20 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{1-20} alkynyl"). In certain embodiments, a heteroalkynyl group refers to a group having from 1 to 10 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{1-10} alkynyl"). In some embodiments, a heteroalkynyl group has 1 to 9 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{1-9} alkynyl"). In some embodiments, a heteroalkynyl group has 1 to 8 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{1-8} alkynyl"). In some embodiments, a heteroalkynyl group has 1 to 7 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{1-7} alkynyl"). In some embodiments, a heteroalkynyl group has 1 to 6 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{1-6} alkynyl"). In some embodiments, a heteroalkynyl group has 1 to 5 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{1-5} alkynyl"). In some embodiments, a heteroalkynyl group has 1 to 4 carbon atoms, at least one triple bond, and 1or 2 heteroatoms within the parent chain ("heteroC_{1-4} alkynyl"). In some embodiments, a heteroalkynyl group has 1 to 3 carbon atoms, at least one triple bond, and 1 heteroatom within the parent chain ("heteroC_{1-3} alkynyl"). In some embodiments, a heteroalkynyl group has 1 to 2 carbon atoms, at least one triple bond, and 1 heteroatom within the parent chain ("heteroC_{1-2} alkynyl"). In some embodiments, a heteroalkynyl group has 1 to 6 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{1-6} alkynyl"). Unless otherwise specified, each instance of a heteroalkynyl group is independently unsubstituted (an "unsubstituted heteroalkynyl") or substituted (a "substituted heteroalkynyl") with one or more substituents. In certain embodiments, the heteroalkynyl group is an unsubstituted heteroC_{1-20} alkynyl. In certain embodiments, the heteroalkynyl group is a substituted heteroC_{1-20} alkynyl.

[028] The term "carbocyclyl" or "carbocyclic" refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 14 ring carbon atoms ("C_{3-14} carbocyclyl") and zero heteroatoms in the non-aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 14 ring carbon atoms ("C_{3-14} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 13 ring carbon atoms ("C_{3-13} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 12 ring carbon atoms ("C_{3-12} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 11 ring carbon atoms ("C_{3-11} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to

10 ring carbon atoms ("C_{3-10} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms ("C_{3-8} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 7 ring carbon atoms ("C_{3-7} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 4 to 6 ring carbon atoms ("C_{4-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 6 ring carbon atoms ("C_{5-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C_{5-10} carbocyclyl"). Exemplary C_{3-6} carbocyclyl groups include cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Exemplary C_{3-8} carbocyclyl groups include the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), and the like. Exemplary C_{3-10} carbocyclyl groups include the aforementioned C_{3-8} carbocyclyl groups as well as cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), spiro[4.5]decanyl (C_{10}), and the like. Exemplary C_{3-8} carbocyclyl groups include the aforementioned C_{3-10} carbocyclyl groups as well as cycloundecyl (C_{11}), spiro[5.5]undecanyl (C_{11}), cyclododecyl (C_{12}), cyclododecenyl (C_{12}), cyclotridecane (C_{13}), cyclotetradecane (C_{14}), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic ("monocyclic carbocyclyl") or polycyclic (*e.g.*, containing a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic carbocyclyl") or tricyclic system ("tricyclic carbocyclyl")) and can be saturated or can contain one or more carbon-carbon double or triple bonds. "Carbocyclyl" also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. Unless otherwise specified, each instance of a carbocyclyl group is independently unsubstituted (an "unsubstituted carbocyclyl") or substituted (a "substituted carbocyclyl") with one or more substituents. In certain embodiments, the carbocyclyl group is an unsubstituted C_{3-14} carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C_{3-14} carbocyclyl.

[029] In some embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 14 ring carbon atoms ("C_{3-14} cycloalkyl"). In some embodiments, a cycloalkyl group

has 3 to 10 ring carbon atoms ("C_{3-10} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C_{3-8} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C_{3-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 4 to 6 ring carbon atoms ("C_{4-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms ("C_{5-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms ("C_{5-10} cycloalkyl"). Examples of C_{5-6} cycloalkyl groups include cyclopentyl (C_5) and cyclohexyl (C_5). Examples of C_{3-6} cycloalkyl groups include the aforementioned C_{5-6} cycloalkyl groups as well as cyclopropyl (C_3) and cyclobutyl (C_4). Examples of C_{3-8} cycloalkyl groups include the aforementioned C_{3-6} cycloalkyl groups as well as cycloheptyl (C_7) and cyclooctyl (C_8). Unless otherwise specified, each instance of a cycloalkyl group is independently unsubstituted (an "unsubstituted cycloalkyl") or substituted (a "substituted cycloalkyl") with one or more substituents. In certain embodiments, the cycloalkyl group is an unsubstituted C_{3-14} cycloalkyl. In certain embodiments, the cycloalkyl group is a substituted C_{3-14} cycloalkyl. In certain embodiments, the carbocyclyl includes 0, 1, or 2 C=C double bonds in the carbocyclic ring system, as valency permits.

[030] The term "heterocyclyl" or "heterocyclic" refers to a radical of a 3- to 14-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("3–14 membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or polycyclic (*e.g.*, a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic heterocyclyl") or tricyclic system ("tricyclic heterocyclyl")), and can be saturated or can contain one or more carbon-carbon double or triple bonds. Heterocyclyl polycyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. Unless otherwise specified, each instance of heterocyclyl is independently unsubstituted (an "unsubstituted heterocyclyl") or

substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is an unsubstituted 3–14 membered heterocyclyl. In certain embodiments, the heterocyclyl group is a substituted 3–14 membered heterocyclyl. In certain embodiments, the heterocyclyl is substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclyl, wherein 1, 2, or 3 atoms in the heterocyclic ring system are independently oxygen, nitrogen, or sulfur, as valency permits.

[031] In some embodiments, a heterocyclyl group is a 5–10 membered non-aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–10 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–8 membered non-aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–8 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–6 membered non-aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–6 membered heterocyclyl"). In some embodiments, the 5–6 membered heterocyclyl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur.

[032] Exemplary 3-membered heterocyclyl groups containing 1 heteroatom include azirdinyl, oxiranyl, and thiiranyl. Exemplary 4-membered heterocyclyl groups containing 1 heteroatom include azetidinyl, oxetanyl, and thietanyl. Exemplary 5-membered heterocyclyl groups containing 1 heteroatom include tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing 2 heteroatoms include dioxolanyl, oxathiolanyl and dithiolanyl. Exemplary 5-membered heterocyclyl groups containing 3 heteroatoms include triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing 1 heteroatom include piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6-membered heterocyclyl groups containing 2 heteroatoms include piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6-membered heterocyclyl groups containing 3 heteroatoms include triazinyl. Exemplary 7-membered heterocyclyl groups containing 1

heteroatom include azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing 1 heteroatom include azocanyl, oxecanyl and thiocanyl. Exemplary bicyclic heterocyclyl groups include indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, tetrahydrobenzothienyl, tetrahydrobenzofuranyl, tetrahydroindolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, decahydroisoquinolinyl, octahydrochromenyl, octahydroisochromenyl, decahydronaphthyridinyl, decahydro-1,8-naphthyridinyl, octahydropyrrolo[3,2-b]pyrrole, indolinyl, phthalimidyl, naphthalimidyl, chromanyl, chromenyl, 1H-benzo[e][1,4]diazepinyl, 1,4,5,7-tetrahydropyrano[3,4-b]pyrrolyl, 5,6-dihydro-4H-furo[3,2-b]pyrrolyl, 6,7-dihydro-5H-furo[3,2-b]pyranyl, 5,7-dihydro-4H-thieno[2,3-c]pyranyl, 2,3-dihydro-1H-pyrrolo[2,3-b]pyridinyl, 2,3-dihydrofuro[2,3-b]pyridinyl, 4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridinyl, 4,5,6,7-tetrahydrofuro[3,2-c]pyridinyl, 4,5,6,7-tetrahydrothieno[3,2-b]pyridinyl, 1,2,3,4-tetrahydro-1,6-naphthyridinyl, and the like.

[033] The term "aryl" refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_{6-14} aryl"). In some embodiments, an aryl group has 6 ring carbon atoms ("C_6 aryl"; *e.g.*, phenyl). In some embodiments, an aryl group has 10 ring carbon atoms ("C_{10} aryl"; *e.g.*, naphthyl such as 1–naphthyl and 2-naphthyl). In some embodiments, an aryl group has 14 ring carbon atoms ("C_{14} aryl"; *e.g.*, anthracyl). "Aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Unless otherwise specified, each instance of an aryl group is independently unsubstituted (an "unsubstituted aryl") or substituted (a "substituted aryl") with one or more substituents. In certain embodiments, the aryl group is an unsubstituted C_{6-14} aryl. In certain embodiments, the aryl group is a substituted C_{6-14} aryl.

[034] "Aralkyl" is a subset of "alkyl" and refers to an alkyl group substituted by an aryl group, wherein the point of attachment is on the alkyl moiety.

[035] The term "heteroaryl" refers to a radical of a 5-14 membered monocyclic or polycyclic (*e.g.*, bicyclic, tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic

ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-14 membered heteroaryl"). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl polycyclic ring systems can include one or more heteroatoms in one or both rings. "Heteroaryl" includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused polycyclic (aryl/heteroaryl) ring system. Polycyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *e.g.*, either the ring bearing a heteroatom (*e.g.*, 2-indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5-indolyl). In certain embodiments, the heteroaryl is substituted or unsubstituted, 5- or 6-membered, monocyclic heteroaryl, wherein 1, 2, 3, or 4 atoms in the heteroaryl ring system are independently oxygen, nitrogen, or sulfur. In certain embodiments, the heteroaryl is substituted or unsubstituted, 9- or 10-membered, bicyclic heteroaryl, wherein 1, 2, 3, or 4 atoms in the heteroaryl ring system are independently oxygen, nitrogen, or sulfur.

[036] In some embodiments, a heteroaryl group is a 5-10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5-8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5-6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-6 membered heteroaryl"). In some embodiments, the 5-6 membered heteroaryl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In

some embodiments, the 5-6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Unless otherwise specified, each instance of a heteroaryl group is independently unsubstituted (an "unsubstituted heteroaryl") or substituted (a "substituted heteroaryl") with one or more substituents. In certain embodiments, the heteroaryl group is an unsubstituted 5-14 membered heteroaryl. In certain embodiments, the heteroaryl group is a substituted 5-14 membered heteroaryl.

[037] Exemplary 5-membered heteroaryl groups containing 1 heteroatom include pyrrolyl, furanyl, and thiophenyl. Exemplary 5-membered heteroaryl groups containing 2 heteroatoms include imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing 3 heteroatoms include triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing 4 heteroatoms include tetrazolyl. Exemplary 6-membered heteroaryl groups containing 1 heteroatom include pyridinyl. Exemplary 6-membered heteroaryl groups containing 2 heteroatoms include pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing 3 or 4 heteroatoms include triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing 1 heteroatom include azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl. Exemplary tricyclic heteroaryl groups include phenanthridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenothiazinyl, phenoxazinyl, and phenazinyl.

[038] "Heteroaralkyl" is a subset of "alkyl" and refers to an alkyl group substituted by a heteroaryl group, wherein the point of attachment is on the alkyl moiety.

[039] The term "unsaturated bond" refers to a double or triple bond.

[040] The term "unsaturated" or "partially unsaturated" refers to a moiety that includes at least one double or triple bond.

[041] The term "saturated" or "fully saturated" refers to a moiety that does not contain a double or triple bond, *e.g.*, the moiety only contains single bonds.

[042] The term "halo" or "halogen" refers to fluorine (fluoro, –F), chlorine (chloro, –Cl), bromine (bromo, –Br), or iodine (iodo, –I).

[043] The term "hydroxyl" or "hydroxy" refers to the group –OH. The term "substituted hydroxyl" or "substituted hydroxyl," by extension, refers to a hydroxyl group wherein the oxygen atom directly attached to the parent molecule is substituted with a group other than hydrogen.

[044] The term "thiol" or "thio" refers to the group –SH. The term "substituted thiol" or "substituted thio," by extension, refers to a thiol group wherein the sulfur atom directly attached to the parent molecule is substituted with a group other than hydrogen.

[045] The term "amino" refers to the group $–NH_2$. The term "substituted amino," by extension, refers to a monosubstituted amino, a disubstituted amino, or a trisubstituted amino. In certain embodiments, the "substituted amino" is a monosubstituted amino or a disubstituted amino group. The term "monosubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with one hydrogen and one group other than hydrogen. The term "disubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with two groups other than hydrogen. The term "trisubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with three non-hydrogen groups.

[046] Affixing the suffix "-ene" to a group indicates the group is a divalent moiety, *e.g.*, alkylene is an optionally substituted divalent moiety of alkyl (*e.g.*, unsubstituted C_6 alkylene is represented by $–(CH_2)_6–$) and heteroalkylene is the divalent moiety of heteroalkyl (*e.g.*, unsubstituted hetero-C_6-alkylene is represented by, for example, $–(CH_2)$-O-$(CH_2)_5–$).

[047] A group is optionally substituted unless expressly provided otherwise. The term "optionally substituted" refers to being substituted or unsubstituted. In certain embodiments, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups are optionally substituted. "Optionally substituted" refers to a group which is substituted or unsubstituted (*e.g.*, "substituted" or "unsubstituted" alkyl, "substituted" or "unsubstituted" alkenyl, "substituted" or "unsubstituted" alkynyl, "substituted" or "unsubstituted" heteroalkyl, "substituted" or "unsubstituted" heteroalkenyl, "substituted" or "unsubstituted" heteroalkynyl, "substituted" or "unsubstituted" carbocyclyl, "substituted" or "unsubstituted" heterocyclyl, "substituted" or "unsubstituted" aryl or "substituted" or

"unsubstituted" heteroaryl group). In general, the term "substituted" means that at least one hydrogen present on a group is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term "substituted" is contemplated to include substitution with all permissible substituents of organic compounds, and includes any of the substituents described herein that results in the formation of a stable compound. The present invention contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety. The invention is not limited in any manner by the exemplary substituents described herein.

[048] Exemplary substituents include halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{aa}$, $-ON(R^{bb})_2$, $-N(R^{bb})_2$, $-N(R^{bb})_3^+X^-$, $-SH$, $-SR^{aa}$, $-C(=O)H$, $-C(=O)R^{aa}$, $-CO_2H$, $-CO_2R^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, $-NR^{bb}SO_2R^{aa}$, $-SO_2N(R^{bb})_2$, $-SO_2R^{aa}$, $-SO_2OR^{aa}$, $-OSO_2R^{aa}$, $-S(=O)R^{aa}$, $-OS(=O)R^{aa}$, $-C(=O)SR^{aa}$, $-SC(=O)SR^{aa}$, $-OC(=O)SR^{aa}$, $-SC(=O)OR^{aa}$, $-SC(=O)R^{aa}$, C_{1-20} alkyl, C_{1-20} perhaloalkyl, C_{1-20} alkenyl, C_{1-20} alkynyl, heteroC_{1-20} alkyl, heteroC_{1-20} alkenyl, heteroC_{1-20} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl;

or two geminal hydrogens on a carbon atom are replaced with the group =O or =S, wherein:

each instance of R^{aa} is, independently, selected from C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, heteroC_{1-6} alkyl, heteroC_{1-6}alkenyl, heteroC_{1-6}alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{aa} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring;

each instance of R^{bb} is, independently, selected from hydrogen, $-OH$, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$,

$-C(=O)SR^{cc}$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, heteroC_{1-6}alkyl, heteroC_{1-6}alkenyl, heteroC_{1-6}alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl;

each instance of R^{cc} is, independently, selected from hydrogen, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, heteroC_{1-6} alkyl, heteroC_{1-6} alkenyl, heteroC_{1-6} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl; and

each X^- is a counterion.

[049] In certain embodiments, each substituent is independently halogen, substituted or unsubstituted C_{1-6} alkyl, $-OR^{aa}$, $-SR^{aa}$, $-N(R^{bb})_2$, $-CN$, $-SCN$, $-NO_2$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, or $-NR^{bb}C(=O)N(R^{bb})_2$. In certain embodiments, each substituent is independently halogen, substituted or unsubstituted C_{1-6} alkyl, $-OR^{aa}$, $-SR^{aa}$, $-N(R^{bb})_2$, $-CN$, $-SCN$, $-NO_2$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, or $-NR^{bb}C(=O)N(R^{bb})_2$, wherein R^{aa} is hydrogen, substituted or unsubstituted C_{1-10} alkyl, an oxygen protecting group (*e.g.*, silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, t-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl) when attached to an oxygen atom, or a sulfur protecting group (*e.g.*, acetamidomethyl, t-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl) when attached to a sulfur atom; and each R^{bb} is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, or a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts). In certain embodiments, each substituent is independently halogen, substituted or unsubstituted C_{1-6} alkyl, $-OR^{aa}$, $-N(R^{bb})_2$, $-CN$, or $-NO_2$.

[050] In certain embodiments, each substituent is independently halogen, substituted or unsubstituted C_{1-10} alkyl, $-OR^{aa}$, $-SR^{aa}$, $-N(R^{bb})_2$, $-CN$, $-SCN$, or $-NO_2$, wherein R^{aa} is hydrogen, substituted or unsubstituted C_{1-10} alkyl, an oxygen protecting group (*e.g.*, silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, t-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl) when attached to an oxygen atom, or a sulfur protecting group (*e.g.*, acetamidomethyl, t-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl) when attached to a sulfur atom; and each R^{bb} is independently hydrogen, substituted or unsubstituted C_{1-10} alkyl, or a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[051] In certain embodiments, each nitrogen atom substituent is independently substituted or unsubstituted C_{1-6} alkyl, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, or a nitrogen protecting group.

[052] Nitrogen protecting groups include $-OH$, $-OR^{aa}$, $-N(R^{cc})_2$, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-C(=NR^{cc})R^{aa}$, $-C(=NR^{cc})OR^{aa}$, $-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, C_{1-10} alkyl (*e.g.*, aralkyl, heteroaralkyl), C_{1-20} alkenyl, C_{1-20} alkynyl, hetero C_{1-20} alkyl, hetero C_{1-20} alkenyl, hetero C_{1-20} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl groups, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aralkyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined herein. Nitrogen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference. In certain embodiments, at least one nitrogen protecting group is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts.

[053] In certain embodiments, each oxygen atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-10} alkyl, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, or an oxygen protecting group.

[054] Oxygen protecting groups include $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3{}^+X^-$, $-P(OR^{cc})_2$, $-P(OR^{cc})_3{}^+X^-$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, and $-P(=O)(N(R^{bb})_2)_2$, wherein X^-, R^{aa}, R^{bb}, and R^{cc} are as defined herein. Oxygen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference. In certain embodiments, at least one oxygen protecting group is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, t-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl.

[055] The term "silyl" refers to the group $-Si(R^{aa})_3$, wherein R^{aa} is as defined herein.

[056] In certain embodiments, each sulfur atom substituent is independently substituted or unsubstituted C_{1-10} alkyl, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, or a sulfur protecting group.

[057] In some embodiments, each sulfur protecting group is selected from the group consisting of $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3{}^+X^-$,

$-P(OR^{cc})_2$, $-P(OR^{cc})_3{}^+X^-$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, and $-P(=O)(N(R^{bb})_2)_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein. Sulfur protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[058] A "counterion" or "anionic counterion" is a negatively charged group associated with a positively charged group in order to maintain electronic neutrality. An anionic counterion may be monovalent (*e.g.*, including one formal negative charge). An anionic counterion may also be multivalent (*e.g.*, including more than one formal negative charge), such as divalent or trivalent. Exemplary counterions include halide ions (*e.g.*, F^-, Cl^-, Br^-, I^-), NO_3^-, ClO_4^-, OH^-, $H_2PO_4^-$, HCO_3^-, HSO_4^-, sulfonate ions (*e.g.*, methansulfonate, trifluoromethanesulfonate, *p*–toluenesulfonate, benzenesulfonate, 10–camphor sulfonate, naphthalene–2–sulfonate, naphthalene–1–sulfonic acid–5–sulfonate, ethan–1–sulfonic acid–2–sulfonate, and the like), carboxylate ions (*e.g.*, acetate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, gluconate, and the like), BF_4^-, PF_4^-, PF_6^-, AsF_6^-, SbF_6^-, $B[3,5\text{-}(CF_3)_2C_6H_3]_4]^-$, $B(C_6F_5)_4^-$, BPh_4^-, $Al(OC(CF_3)_3)_4^-$, and carborane anions (*e.g.*, $CB_{11}H_{12}^-$ or $(HCB_{11}Me_5Br_6)^-$). Exemplary counterions which may be multivalent include CO_3^{2-}, HPO_4^{2-}, PO_4^{3-}, $B_4O_7^{2-}$, SO_4^{2-}, $S_2O_3^{2-}$, carboxylate anions (*e.g.*, tartrate, citrate, fumarate, maleate, malate, malonate, gluconate, succinate, glutarate, adipate, pimelate, suberate, azelate, sebacate, salicylate, phthalates, aspartate, glutamate, and the like), and carboranes.

[059] Use of the phrase "at least one instance" refers to 1, 2, 3, 4, or more instances, but also encompasses a range, *e.g.*, for example, from 1 to 4, from 1 to 3, from 1 to 2, from 2 to 4, from 2 to 3, or from 3 to 4 instances, inclusive.

[060] A "non-hydrogen group" refers to any group that is defined for a particular variable that is not hydrogen.

[061] As used herein, the term "salt" refers to any and all salts, and encompasses pharmaceutically acceptable salts. Salts include ionic compounds that result from the neutralization reaction of an acid and a base. A salt is composed of one or more cations (positively charged ions) and one or more anions (negative ions) so that the salt is electrically neutral (without a net charge). Salts of the compounds of this invention include those derived from inorganic and organic acids and bases. Examples of acid addition salts are salts of an amino group formed with inorganic acids, such as hydrochloric acid, hydrobromic acid, phosphoric

acid, sulfuric acid, and perchloric acid, or with organic acids, such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods known in the art such as ion exchange. Other salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate, hippurate, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}$ alkyl$)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further salts include ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[062] The term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.* describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid or with organic acids, such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods known in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate,

glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium, and $N^+(C_{1-4}$ alkyl$)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[063] The terms "composition" and "formulation" are used interchangeably.

[064] A "subject" to which administration is contemplated refers to a human (*i.e.*, male or female of any age group, *e.g.*, pediatric subject (*e.g.*, infant, child, or adolescent) or adult subject (*e.g.*, young adult, middle-aged adult, or senior adult)) or non-human animal. In certain embodiments, the non-human animal is a mammal (*e.g.*, primate (*e.g.*, cynomolgus monkey or rhesus monkey), commercially relevant mammal (*e.g.*, cattle, pig, horse, sheep, goat, cat, or dog), or bird (*e.g.*, commercially relevant bird, such as chicken, duck, goose, or turkey)). In certain embodiments, the non-human animal is a fish, reptile, or amphibian. The non-human animal may be a male or female at any stage of development. The non-human animal may be a transgenic animal or genetically engineered animal. The term "patient" refers to a human subject in need of treatment of a disease.

[065] The term "administer," "administering," or "administration" refers to implanting, absorbing, ingesting, injecting, inhaling, or otherwise introducing a compound described herein, or a composition thereof, in or on a subject.

[066] The terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease described herein. In some embodiments, treatment may be administered after one or more signs or symptoms of the disease have developed or have been observed. In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease. For example, treatment may be administered to a susceptible subject prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or

in light of exposure to a pathogen). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

[067] The terms "condition," "disease," and "disorder" are used interchangeably.

[068] An "effective amount" of a compound described herein refers to an amount sufficient to elicit the desired biological response. An effective amount of a compound described herein may vary depending on such factors as the desired biological endpoint, severity of side effects, disease, or disorder, the identity, pharmacokinetics, and pharmacodynamics of the particular compound, the condition being treated, the mode, route, and desired or required frequency of administration, the species, age and health or general condition of the subject. In certain embodiments, an effective amount is a therapeutically effective amount. In certain embodiments, an effective amount is a prophylactic treatment. In certain embodiments, an effective amount is the amount of a compound described herein in a single dose. In certain embodiments, an effective amount is the combined amounts of a compound described herein in multiple doses. In certain embodiments, the desired dosage is delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage is delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

[069] In certain embodiments, an effective amount of a compound for administration one or more times a day to a 70 kg adult human comprises about 0.0001 mg to about 3000 mg, about 0.0001 mg to about 2000 mg, about 0.0001 mg to about 1000 mg, about 0.001 mg to about 1000 mg, about 0.01 mg to about 1000 mg, about 0.1 mg to about 1000 mg, about 1 mg to about 1000 mg, about 1 mg to about 100 mg, about 10 mg to about 1000 mg, or about 100 mg to about 1000 mg, of a compound per unit dosage form.

[070] In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels sufficient to deliver from about 0.001 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, preferably from about 0.1 mg/kg to about 40 mg/kg, preferably from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, and more preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[071] It will be appreciated that dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

[072] A "therapeutically effective amount" of a compound described herein is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to delay or minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms, signs, or causes of the condition, and/or enhances the therapeutic efficacy of another therapeutic agent. In certain embodiments, a therapeutically effective amount is an amount sufficient for treating a disease associated with sigma receptor. In certain embodiments, a therapeutically effective amount is an amount sufficient for binding sigma receptors. In certain embodiments, a therapeutically effective amount is an amount sufficient for treating stimulant (*e.g.*, psychostimulant) abuse, addiction, or dependence. In some embodiments, a therapeutically effective amount is an amount sufficient for treating a neurological disease, a proliferative disease, a painful condition, or a psychiatric disorder. In some embodiments, a therapeutically effective amount is an amount sufficient for treating pain, a neurodegenerative disorder (*e.g.*, Alzheimer's disease, Parkinson's disease), substance addiction, cancer, depression, schizophrenia, anxiety, stroke, obsessive compulsive disorder, or multiple sclerosis.

[073] The term "prevent," "preventing," or "prevention" refers to a prophylactic treatment of a subject who is not and was not with a disease but is at risk of developing the disease or who was with a disease, is not with the disease, but is at risk of regression of the disease. In certain embodiments, the subject is at a higher risk of developing the disease or at a higher risk of regression of the disease than an average healthy member of a population.

[074] As used herein the term "inhibit" or "inhibition" in the context of protein(s), for example, in the context of sigma receptors, refers to a reduction in the activity of the protein. In some embodiments, the term refers to a reduction of the level of protein(s) activity, *e.g.*, (sigma receptor) activity, to a level that is statistically significantly lower than an initial level, which

may, for example, be a baseline level of protein activity. In some embodiments, the term refers to a reduction of the level of protein activity, *e.g.*, sigma receptor activity, to a level that is less than 75%, less than 50%, less than 40%, less than 30%, less than 25%, less than 20%, less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than 0.5%, less than 0.1%, less than 0.01%, less than 0.001%, or less than 0.0001% of an initial level, which may, for example, be a baseline level of protein activity.

[075] The term "sigma receptor" or "σ-receptors" are protein cell surface receptors. There are two subtypes of sigma receptors: sigma-1 (σ_1) and sigma-2 (σ_2). Sigma receptors are a well-defined unique class of receptors, distinct from opioid receptors and phencyclidine binding sites (though originally sigma receptors were in fact thought to be opioid receptors). Various moieties are known to bind to sigma receptors including, for example, cocaine, methamphetamine, morphine, diacetylmorphine, opipramol, PCP, fluvoxamine, berberine, and dextromethorphan.

[076] The terms "substance abuse disorders" and "substance use disorder" are used interchangeably to refer to a mental disorder affecting a person's brain and behavior, resulting in the inability to control their use of substances, including psychoactive substances either licit or illicit (*e.g.*, cocaine, methamphetamine, ecstasy, alcohol, opioids, stimulants, psychedelics). Severe substance use disorders may be referred to as addictions.

[077] The terms "substance addiction" refers to severe forms of substance use disorders. Substance addiction is a progressive disease resulting in losing control of the use of one or more substances (*e.g.*, drugs, pharmaceuticals/medications, stimulants) despite consequences of that use. A disease of the mind characterized by compulsive engagement in rewarding or addictive stimuli. An addiction often involves addictive stimuli that are reinforcing (*e.g.*, increase the likelihood that a person will seek repeated exposure to the agent causing the stimulus) and intrinsically rewarding (*e.g.*, they are perceived by a person as being inherently desirable, positive, and pleasurable). The addiction may arise through transcriptional or epigenetic mechanisms and generally develops over time as a result of persistent exposure to addictive stimulus or stimuli. Cognitive control, particularly inhibitory control over behavior, is impaired in a person suffering from addiction. Additionally, stimulus-driven behavioral responses (i.e., stimulus control) that are associated with a particular rewarding stimulus tend to dominate the behavior of a person suffering from addiction. The term addiction encompasses addiction to

drugs (*e.g.*, cocaine, opioids, and the like), alcohol, gambling, etc. In certain embodiments, the addiction is a drug addiction. In certain embodiments, the addiction is a cocaine addiction. In certain embodiments, the addiction is a methamphetamine addiction. In certain embodiments the addiction is an ecstasy addiction. In certain embodiments, the addiction is an ethanol addiction. In certain embodiments, the addiction is an opioid addiction.

[078] The terms "substance intake" refers to the consumption of substances (*e.g.*, drugs, pharmaceuticals/medications, stimulants).

[079] The term "substance" as used herein refers to psychoactive compounds or molecules. Psychoactive compounds and molecules change nervous system function (*i.e.*, brain function) and result in alterations in mood, awareness, thoughts, feelings, and/or behavior. As used herein, common substances include drugs, pharmaceuticals/medications, and other stimulants, including but not limited to, alcohol, caffeine, nicotine, marijuana, certain pain medicines, heroin, LSD, cocaine, and amphetamines (*e.g.*, methamphetamine, 3,4-methylenedioxymethamphetamine, cathinone). In some embodiments, the substance is methamphetamine or cocaine.

[080] The term "stimulant" refers to compounds/molecules that increase activity of the central nervous system and/or body, are pleasurable and invigorating, and/or have sympathomimetic effects. A non-exhaustive list of exemplary stimulants include methylphenidate, amphetamines (*e.g.*, methamphetamine), and cocaine. In some embodiments, the stimulant is methamphetamine or cocaine.

[081] A "proliferative disease" refers to a disease that occurs due to abnormal growth or extension by the multiplication of cells (Walker, *Cambridge Dictionary of Biology*; Cambridge University Press: Cambridge, UK, 1990). A proliferative disease may be associated with: 1) the pathological proliferation of normally quiescent cells; 2) the pathological migration of cells from their normal location (*e.g.*, metastasis of neoplastic cells); 3) the pathological expression of proteolytic enzymes such as the matrix metalloproteinases (*e.g.*, collagenases, gelatinases, and elastases); or 4) the pathological angiogenesis as in proliferative retinopathy and tumor metastasis. Exemplary proliferative diseases include cancers (*i.e.*, "malignant neoplasms"), benign neoplasms, angiogenesis, inflammatory diseases, and autoimmune diseases.

[082] The term "angiogenesis" refers to the physiological process through which new blood vessels form from pre-existing vessels. Angiogenesis is distinct from vasculogenesis, which is the *de novo* formation of endothelial cells from mesoderm cell precursors. The first vessels in a

developing embryo form through vasculogenesis, after which angiogenesis is responsible for most blood vessel growth during normal or abnormal development. Angiogenesis is a vital process in growth and development, as well as in wound healing and in the formation of granulation tissue. However, angiogenesis is also a fundamental step in the transition of tumors from a benign state to a malignant one, leading to the use of angiogenesis inhibitors in the treatment of cancer. Angiogenesis may be chemically stimulated by angiogenic proteins, such as growth factors (*e.g.*, VEGF). "Pathological angiogenesis" refers to abnormal (*e.g.*, excessive or insufficient) angiogenesis that amounts to and/or is associated with a disease.

[083] The terms "neoplasm" and "tumor" are used herein interchangeably and refer to an abnormal mass of tissue wherein the growth of the mass surpasses and is not coordinated with the growth of a normal tissue. A neoplasm or tumor may be "benign" or "malignant," depending on the following characteristics: degree of cellular differentiation (including morphology and functionality), rate of growth, local invasion, and metastasis. A "benign neoplasm" is generally well differentiated, has characteristically slower growth than a malignant neoplasm, and remains localized to the site of origin. In addition, a benign neoplasm does not have the capacity to infiltrate, invade, or metastasize to distant sites. Exemplary benign neoplasms include, but are not limited to, lipoma, chondroma, adenomas, acrochordon, senile angiomas, seborrheic keratoses, lentigos, and sebaceous hyperplasias. In some cases, certain "benign" tumors may later give rise to malignant neoplasms, which may result from additional genetic changes in a subpopulation of the tumor's neoplastic cells, and these tumors are referred to as "pre-malignant neoplasms." An exemplary pre-malignant neoplasm is a teratoma. In contrast, a "malignant neoplasm" is generally poorly differentiated (anaplasia) and has characteristically rapid growth accompanied by progressive infiltration, invasion, and destruction of the surrounding tissue. Furthermore, a malignant neoplasm generally has the capacity to metastasize to distant sites. The term "metastasis," "metastatic," or "metastasize" refers to the spread or migration of cancerous cells from a primary or original tumor to another organ or tissue and is typically identifiable by the presence of a "secondary tumor" or "secondary cell mass" of the tissue type of the primary or original tumor and not of that of the organ or tissue in which the secondary (metastatic) tumor is located. For example, a prostate cancer that has migrated to bone is said to be metastasized prostate cancer and includes cancerous prostate cancer cells growing in bone tissue.

[084] The term "cancer" refers to a class of diseases characterized by the development of abnormal cells that proliferate uncontrollably and have the ability to infiltrate and destroy normal body tissues. *See e.g.*, *Stedman's Medical Dictionary*, 25th ed.; Hensyl ed.; Williams & Wilkins: Philadelphia, 1990. Exemplary cancers include, but are not limited to, acoustic neuroma; adenocarcinoma; adrenal gland cancer; anal cancer; angiosarcoma (*e.g.*, lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma); appendix cancer; benign monoclonal gammopathy; biliary cancer (*e.g.*, cholangiocarcinoma); bladder cancer; breast cancer (*e.g.*, adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast); brain cancer (*e.g.*, meningioma, glioblastomas, glioma (*e.g.*, astrocytoma, oligodendroglioma), medulloblastoma); bronchus cancer; carcinoid tumor; cervical cancer (*e.g.*, cervical adenocarcinoma); choriocarcinoma; chordoma; craniopharyngioma; colorectal cancer (*e.g.*, colon cancer, rectal cancer, colorectal adenocarcinoma); connective tissue cancer; epithelial carcinoma; ependymoma; endotheliosarcoma (*e.g.*, Kaposi's sarcoma, multiple idiopathic hemorrhagic sarcoma); endometrial cancer (*e.g.*, uterine cancer, uterine sarcoma); esophageal cancer (*e.g.*, adenocarcinoma of the esophagus, Barrett's adenocarcinoma); Ewing's sarcoma; ocular cancer (*e.g.*, intraocular melanoma, retinoblastoma); familiar hypereosinophilia; gall bladder cancer; gastric cancer (*e.g.*, stomach adenocarcinoma); gastrointestinal stromal tumor (GIST); germ cell cancer; head and neck cancer (*e.g.*, head and neck squamous cell carcinoma, oral cancer (*e.g.*, oral squamous cell carcinoma), throat cancer (*e.g.*, laryngeal cancer, pharyngeal cancer, nasopharyngeal cancer, oropharyngeal cancer)); hematopoietic cancers (*e.g.*, leukemia such as acute lymphocytic leukemia (ALL) (*e.g.*, B-cell ALL, T-cell ALL), acute myelocytic leukemia (AML) (*e.g.*, B-cell AML, T-cell AML), chronic myelocytic leukemia (CML) (*e.g.*, B-cell CML, T-cell CML), and chronic lymphocytic leukemia (CLL) (*e.g.*, B-cell CLL, T-cell CLL)); lymphoma such as Hodgkin lymphoma (HL) (*e.g.*, B-cell HL, T-cell HL) and non-Hodgkin lymphoma (NHL) (*e.g.*, B-cell NHL such as diffuse large cell lymphoma (DLCL) (*e.g.*, diffuse large B-cell lymphoma), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone B-cell lymphomas (*e.g.*, mucosa-associated lymphoid tissue (MALT) lymphomas, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma), primary mediastinal B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma (*i.e.*, Waldenström's macroglobulinemia), hairy cell leukemia (HCL), immunoblastic large cell lymphoma, precursor

B-lymphoblastic lymphoma and primary central nervous system (CNS) lymphoma; and T-cell NHL such as precursor T-lymphoblastic lymphoma/leukemia, peripheral T-cell lymphoma (PTCL) (*e.g.*, cutaneous T-cell lymphoma (CTCL) (*e.g.*, mycosis fungoides, Sezary syndrome), angioimmunoblastic T-cell lymphoma, extranodal natural killer T-cell lymphoma, enteropathy type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, and anaplastic large cell lymphoma); a mixture of one or more leukemia/lymphoma as described above; and multiple myeloma (MM)), heavy chain disease (*e.g.*, alpha chain disease, gamma chain disease, mu chain disease); hemangioblastoma; hypopharynx cancer; inflammatory myofibroblastic tumors; immunocytic amyloidosis; kidney cancer (*e.g.*, nephroblastoma *a.k.a.* Wilms' tumor, renal cell carcinoma); liver cancer (*e.g.*, hepatocellular cancer (HCC), malignant hepatoma); lung cancer (*e.g.*, bronchogenic carcinoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), adenocarcinoma of the lung); leiomyosarcoma (LMS); mastocytosis (*e.g.*, systemic mastocytosis); muscle cancer; myelodysplastic syndrome (MDS); mesothelioma; myeloproliferative disorder (MPD) (*e.g.*, polycythemia vera (PV), essential thrombocytosis (ET), agnogenic myeloid metaplasia (AMM) *a.k.a.* myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)); neuroblastoma; neurofibroma (*e.g.*, neurofibromatosis (NF) type 1 or type 2, schwannomatosis); neuroendocrine cancer (*e.g.*, gastroenteropancreatic neuroendoctrine tumor (GEP-NET), carcinoid tumor); osteosarcoma (*e.g.,* bone cancer); ovarian cancer (*e.g.*, cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma); papillary adenocarcinoma; pancreatic cancer (*e.g.*, pancreatic andenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), Islet cell tumors); penile cancer (*e.g.*, Paget's disease of the penis and scrotum); pinealoma; primitive neuroectodermal tumor (PNT); plasma cell neoplasia; paraneoplastic syndromes; intraepithelial neoplasms; prostate cancer (*e.g.*, prostate adenocarcinoma); rectal cancer; rhabdomyosarcoma; salivary gland cancer; skin cancer (*e.g.*, squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)); small bowel cancer (*e.g.*, appendix cancer); soft tissue sarcoma (*e.g.*, malignant fibrous histiocytoma (MFH), liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma); sebaceous gland carcinoma; small intestine cancer; sweat gland carcinoma; synovioma; testicular cancer (*e.g.*, seminoma, testicular embryonal carcinoma); thyroid cancer (*e.g.*, papillary carcinoma of the thyroid, papillary thyroid

carcinoma (PTC), medullary thyroid cancer); urethral cancer; vaginal cancer; and vulvar cancer (*e.g.*, Paget's disease of the vulva).

[085] A "painful condition" includes, but is not limited to, neuropathic pain (*e.g.,* peripheral neuropathic pain), central pain, deafferentiation pain, chronic pain (*e.g.*, chronic nociceptive pain, and other forms of chronic pain such as post–operative pain, *e.g.,* pain arising after hip, knee, or other replacement surgery), pre–operative pain, stimulus of nociceptive receptors (nociceptive pain), acute pain (*e.g.*, phantom and transient acute pain), noninflammatory pain, inflammatory pain, pain associated with cancer, wound pain, burn pain, postoperative pain, pain associated with medical procedures, pain resulting from pruritus, painful bladder syndrome, pain associated with premenstrual dysphoric disorder and/or premenstrual syndrome, pain associated with chronic fatigue syndrome, pain associated with pre–term labor, pain associated with withdrawal symptoms from drug addiction, joint pain, arthritic pain (*e.g.*, pain associated with crystalline arthritis, osteoarthritis, psoriatic arthritis, gouty arthritis, reactive arthritis, rheumatoid arthritis or Reiter's arthritis), lumbosacral pain, musculo–skeletal pain, headache, migraine, muscle ache, lower back pain, neck pain, toothache, dental/maxillofacial pain, visceral pain and the like. One or more of the painful conditions contemplated herein can comprise mixtures of various types of pain provided above and herein (*e.g.* nociceptive pain, inflammatory pain, neuropathic pain, *etc.*). In some embodiments, a particular painful condition can dominate. In other embodiments, the painful condition comprises two or more types of painful conditions without one dominating. A skilled clinician can determine the dosage to achieve a therapeutically effective amount for a particular subject based on the pain.

[086] In certain embodiments, the painful condition is neuropathic pain. The term "neuropathic pain" refers to pain resulting from injury to a nerve. Neuropathic pain is distinguished from nociceptive pain, which is the pain caused by acute tissue injury involving small cutaneous nerves or small nerves in muscle or connective tissue. Neuropathic pain typically is long-lasting or chronic and often develops days or months following an initial acute tissue injury. Neuropathic pain can involve persistent, spontaneous pain as well as allodynia, which is a painful response to a stimulus that normally is not painful. Neuropathic pain also can be characterized by hyperalgesia, in which there is an accentuated response to a painful stimulus that usually is trivial, such as a pin prick. Neuropathic pain conditions can develop following neuronal injury and the resulting pain may persist for months or years, even after the original

injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the brain. Neuropathic pain conditions include, but are not limited to, diabetic neuropathy (*e.g.*, peripheral diabetic neuropathy); sciatica; non-specific lower back pain; multiple sclerosis pain; carpal tunnel syndrome, fibromyalgia; HIV-related neuropathy; neuralgia (*e.g.*, post-herpetic neuralgia, trigeminal neuralgia); pain resulting from physical trauma (*e.g.*, amputation; surgery, invasive medical procedures, toxins, burns, infection), pain resulting from cancer or chemotherapy (*e.g.*, chemotherapy-induced pain such as chemotherapy-induced peripheral neuropathy), and pain resulting from an inflammatory condition (*e.g.*, a chronic inflammatory condition). Neuropathic pain can result from a peripheral nerve disorder such as neuroma; nerve compression; nerve crush, nerve stretch or incomplete nerve transection; mononeuropathy or polyneuropathy. Neuropathic pain can also result from a disorder such as dorsal root ganglion compression; inflammation of the spinal cord; contusion, tumor or hemisection of the spinal cord; tumors of the brainstem, thalamus or cortex; or trauma to the brainstem, thalamus or cortex.

[087] The symptoms of neuropathic pain are heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia), or an absence of or deficit in selective sensory pathways (hypoalgesia).

[088] In certain embodiments, the painful condition is non-inflammatory pain. The types of non-inflammatory pain include, without limitation, peripheral neuropathic pain (*e.g.*, pain caused by a lesion or dysfunction in the peripheral nervous system), central pain (*e.g.*, pain caused by a lesion or dysfunction of the central nervous system), deafferentation pain (*e.g.*, pain due to loss of sensory input to the central nervous system), chronic nociceptive pain (*e.g.*, certain types of cancer pain), noxious stimulus of nociceptive receptors (*e.g.*, pain felt in response to tissue damage or impending tissue damage), phantom pain (*e.g.*, pain felt in a part of the body that no longer exists, such as a limb that has been amputated), pain felt by psychiatric subjects (*e.g.*, pain

where no physical cause may exist), and wandering pain (*e.g.*, wherein the pain repeatedly changes location in the body).

[089] The term "neurological disease" refers to any disease of the nervous system, including diseases that involve the central nervous system (brain, brainstem and cerebellum), the peripheral nervous system (including cranial nerves), and the autonomic nervous system (parts of which are located in both central and peripheral nervous system). Neurodegenerative diseases refer to a type of neurological disease marked by the loss of nerve cells, including, but not limited to, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, tauopathies (including frontotemporal dementia), and Huntington's disease. Examples of neurological diseases include, but are not limited to, headache, stupor and coma, dementia, seizure, sleep disorders, trauma, infections, neoplasms, neuro-ophthalmology, movement disorders, demyelinating diseases, spinal cord disorders, and disorders of peripheral nerves, muscle and neuromuscular junctions. Addiction and mental illness, include, but are not limited to, bipolar disorder and schizophrenia, are also included in the definition of neurological diseases. Further examples of neurological diseases include acquired epileptiform aphasia; acute disseminated encephalomyelitis; adrenoleukodystrophy; agenesis of the corpus callosum; agnosia; Aicardi syndrome; Alexander disease; Alpers' disease; alternating hemiplegia; Alzheimer's disease; amyotrophic lateral sclerosis; anencephaly; Angelman syndrome; angiomatosis; anoxia; aphasia; apraxia; arachnoid cysts; arachnoiditis; Arnold-Chiari malformation; arteriovenous malformation; Asperger syndrome; ataxia telangiectasia; attention deficit hyperactivity disorder; autism; autonomic dysfunction; back pain; Batten disease; Behcet's disease; Bell's palsy; benign essential blepharospasm; benign focal; amyotrophy; benign intracranial hypertension; Binswanger's disease; blepharospasm; Bloch Sulzberger syndrome; brachial plexus injury; brain abscess; brain injury; brain tumors (including glioblastoma multiforme); spinal tumor; Brown-Sequard syndrome; Canavan disease; carpal tunnel syndrome (CTS); causalgia; central pain syndrome; central pontine myelinolysis; cephalic disorder; cerebral aneurysm; cerebral arteriosclerosis; cerebral atrophy; cerebral gigantism; cerebral palsy; Charcot-Marie-Tooth disease; chemotherapy-induced neuropathy and neuropathic pain; Chiari malformation; chorea; chronic inflammatory demyelinating polyneuropathy (CIDP); chronic pain; chronic regional pain syndrome; Coffin Lowry syndrome; coma, including persistent vegetative state; congenital facial diplegia; corticobasal degeneration; cranial arteritis; craniosynostosis; Creutzfeldt-Jakob disease;

cumulative trauma disorders; Cushing's syndrome; cytomegalic inclusion body disease (CIBD); cytomegalovirus infection; dancing eyes-dancing feet syndrome; Dandy-Walker syndrome; Dawson disease; De Morsier's syndrome; Dejerine-Klumpke palsy; dementia; dermatomyositis; diabetic neuropathy; diffuse sclerosis; dysautonomia; dysgraphia; dyslexia; dystonias; early infantile epileptic encephalopathy; empty sella syndrome; encephalitis; encephaloceles; encephalotrigeminal angiomatosis; epilepsy; Erb's palsy; essential tremor; Fabry's disease; Fahr's syndrome; fainting; familial spastic paralysis; febrile seizures; Fisher syndrome; Friedreich's ataxia; frontotemporal dementia and other "tauopathies"; Gaucher's disease; Gerstmann's syndrome; giant cell arteritis; giant cell inclusion disease; globoid cell leukodystrophy; Guillain-Barre syndrome; HTLV-1 associated myelopathy; Hallervorden-Spatz disease; head injury; headache; hemifacial spasm; hereditary spastic paraplegia; heredopathia atactica polyneuritiformis; herpes zoster oticus; herpes zoster; Hirayama syndrome; HIV-associated dementia and neuropathy (see also neurological manifestations of AIDS); holoprosencephaly; Huntington's disease and other polyglutamine repeat diseases; hydranencephaly; hydrocephalus; hypercortisolism; hypoxia; immune-mediated encephalomyelitis; inclusion body myositis; incontinentia pigmenti; infantile; phytanic acid storage disease; Infantile Refsum disease; infantile spasms; inflammatory myopathy; intracranial cyst; intracranial hypertension; Joubert syndrome; Kearns-Sayre syndrome; Kennedy disease; Kinsbourne syndrome; Klippel Feil syndrome; Krabbe disease; Kugelberg-Welander disease; kuru; Lafora disease; Lambert-Eaton myasthenic syndrome; Landau-Kleffner syndrome; lateral medullary (Wallenberg) syndrome; learning disabilities; Leigh's disease; Lennox-Gastaut syndrome; Lesch-Nyhan syndrome; leukodystrophy; Lewy body dementia; lissencephaly; locked-in syndrome; Lou Gehrig's disease (aka motor neuron disease or amyotrophic lateral sclerosis); lumbar disc disease; Lyme disease-neurological sequelae; Machado-Joseph disease; macrencephaly; megalencephaly; Melkersson-Rosenthal syndrome; Menieres disease; meningitis; Menkes disease; metachromatic leukodystrophy; microcephaly; migraine; Miller Fisher syndrome; mini-strokes; mitochondrial myopathies; Mobius syndrome; monomelic amyotrophy; motor neurone disease; moyamoya disease; mucopolysaccharidoses; multi-infarct dementia; multifocal motor neuropathy; multiple sclerosis and other demyelinating disorders; multiple system atrophy with postural hypotension; muscular dystrophy; myasthenia gravis; myelinoclastic diffuse sclerosis; myoclonic encephalopathy of infants; myoclonus; myopathy;

myotonia congenital; narcolepsy; neurofibromatosis; neuroleptic malignant syndrome; neurological manifestations of AIDS; neurological sequelae of lupus; neuromyotonia; neuronal ceroid lipofuscinosis; neuronal migration disorders; Niemann-Pick disease; O'Sullivan-McLeod syndrome; occipital neuralgia; occult spinal dysraphism sequence; Ohtahara syndrome; olivopontocerebellar atrophy; opsoclonus myoclonus; optic neuritis; orthostatic hypotension; overuse syndrome; paresthesia; Parkinson's disease; paramyotonia congenita; paraneoplastic diseases; paroxysmal attacks; Parry Romberg syndrome; Pelizaeus-Merzbacher disease; periodic paralyses; peripheral neuropathy; painful neuropathy and neuropathic pain; persistent vegetative state; pervasive developmental disorders; photic sneeze reflex; phytanic acid storage disease; Pick's disease; pinched nerve; pituitary tumors; polymyositis; porencephaly; Post-Polio syndrome; postherpetic neuralgia (PHN); postinfectious encephalomyelitis; postural hypotension; Prader-Willi syndrome; primary lateral sclerosis; prion diseases; progressive; hemifacial atrophy; progressive multifocal leukoencephalopathy; progressive sclerosing poliodystrophy; progressive supranuclear palsy; pseudotumor cerebri; Ramsay-Hunt syndrome (Type I and Type II); Rasmussen's Encephalitis; reflex sympathetic dystrophy syndrome; Refsum disease; repetitive motion disorders; repetitive stress injuries; restless legs syndrome; retrovirus-associated myelopathy; Rett syndrome; Reye's syndrome; Saint Vitus Dance; Sandhoff disease; Schilder's disease; schizencephaly; septo-optic dysplasia; shaken baby syndrome; shingles; Shy-Drager syndrome; Sjogren's syndrome; sleep apnea; Soto's syndrome; spasticity; spina bifida; spinal cord injury; spinal cord tumors; spinal muscular atrophy; stiff-person syndrome; stroke; Sturge-Weber syndrome; subacute sclerosing panencephalitis; subarachnoid hemorrhage; subcortical arteriosclerotic encephalopathy; sydenham chorea; syncope; syringomyelia; tardive dyskinesia; Tay-Sachs disease; temporal arteritis; tethered spinal cord syndrome; Thomsen disease; thoracic outlet syndrome; tic douloureux; Todd's paralysis; Tourette syndrome; transient ischemic attack; transmissible spongiform encephalopathies; transverse myelitis; traumatic brain injury; tremor; trigeminal neuralgia; tropical spastic paraparesis; tuberous sclerosis; vascular dementia (multi-infarct dementia); vasculitis including temporal arteritis; Von Hippel-Lindau Disease (VHL); Wallenberg's syndrome; Werdnig-Hoffman disease; West syndrome; whiplash; Williams syndrome; Wilson's disease; and Zellweger syndrome.

[090] The term "psychiatric disorder" refers to a disease of the mind and includes diseases and disorders listed in the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV), published by the American Psychiatric Association, Washington D. C. (1994). Psychiatric disorders include, but are not limited to, anxiety disorders (*e.g.*, acute stress disorder agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, separation anxiety disorder, social phobia, and specific phobia), childhood disorders, (*e.g.*, attention-deficit/hyperactivity disorder, conduct disorder, and oppositional defiant disorder), eating disorders (*e.g.*, anorexia nervosa and bulimia nervosa), mood disorders (*e.g.*, depression, bipolar disorder, cyclothymic disorder, dysthymic disorder, and major depressive disorder), personality disorders (*e.g.*, antisocial personality disorder, avoidant personality disorder, borderline personality disorder, dependent personality disorder, histrionic personality disorder, narcissistic personality disorder, obsessive-compulsive personality disorder, paranoid personality disorder, schizoid personality disorder, and schizotypal personality disorder), psychotic disorders (*e.g.*, brief psychotic disorder, delusional disorder, schizoaffective disorder, schizophreniform disorder, schizophrenia, and shared psychotic disorder), substance-related disorders (*e.g.*, alcohol dependence, amphetamine dependence, cannabis dependence, cocaine dependence, hallucinogen dependence, inhalant dependence, nicotine dependence, opioid dependence, phencyclidine dependence, and sedative dependence), adjustment disorder, autism, delirium, dementia, multi-infarct dementia, learning and memory disorders (*e.g.*, amnesia and age-related memory loss), and Tourette's disorder.

[091] These and other exemplary substituents are described in more detail in the Detailed Description, Examples, and Claims. The invention is not limited in any manner by the above exemplary listing of substituents or definitions. Additional terms may be defined in other sections of this disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[092] FIG. 1A and 1B show the graphs of *in vivo* plasma and brain concentration of HA134 and CM304 versus time in CD1 mice following 50 mg/Kg oral and 2.5 mg/kg intravenous dose. Shown in FIG. 1A is the data for HA134, and shown in FIG. 1B is the data for CM304.

DETAILED DESCRIPTION

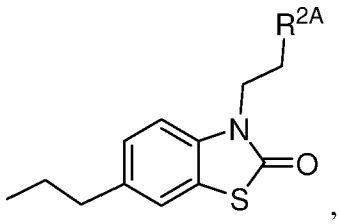
[093] Provided herein are compounds, compositions, methods, uses, and kits comprising compounds as delineated herein, including those of Formula (I), (II), and (III).

[094] In some embodiments, the compounds as delineated herein, including those of Formula (I), (II), and (III) are sigma-receptor antagonist.

[095] In some embodiments, the compounds as delineated herein, including those of Formula (I), (II), and (III) are metabolically stable.

Compounds of Formula (I)

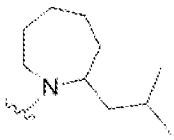
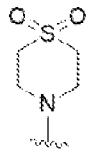
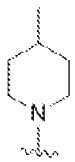
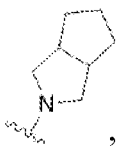
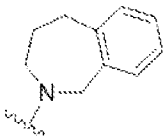
[096] In one aspect, provided herein are compounds of Formula (I):

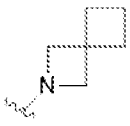
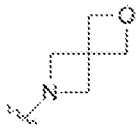
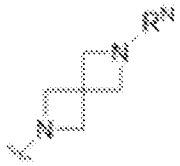
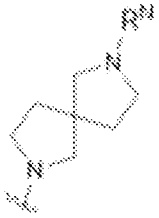
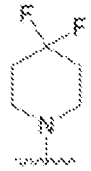


(I)

or pharmaceutically acceptable salt thereof, wherein:

R^{2A} is selected from the group consisting of:

substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or

unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , and substituted or unsubstituted  ;

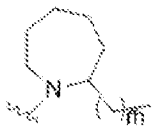
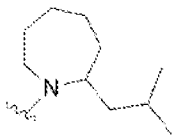
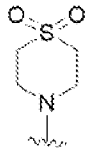
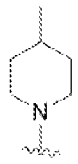
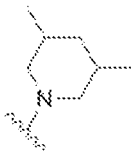
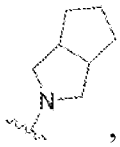
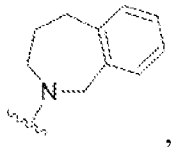
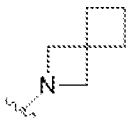
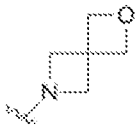
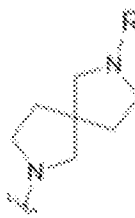
wherein the substituted R^{2A} is substituted with one or more substituents independently selected from halo, C_{1-6} alkyl, -OH, -O(C_{1-6} alkyl), -NH_2, and -NMe_2;

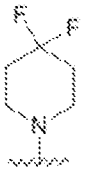
R^N is H, C_{1-6} alkyl, or a nitrogen protecting group; and

m is 1, 2, 3, 4, 5, or 6.

[097] In some embodiments, R^N is H, C_{1-6} alkyl, or a nitrogen protecting group. In some embodiments, R^N is H, methyl, or Boc. In some embodiments, R^N is H. In some embodiments, R^N is methyl. In some embodiments, R^N is Boc.

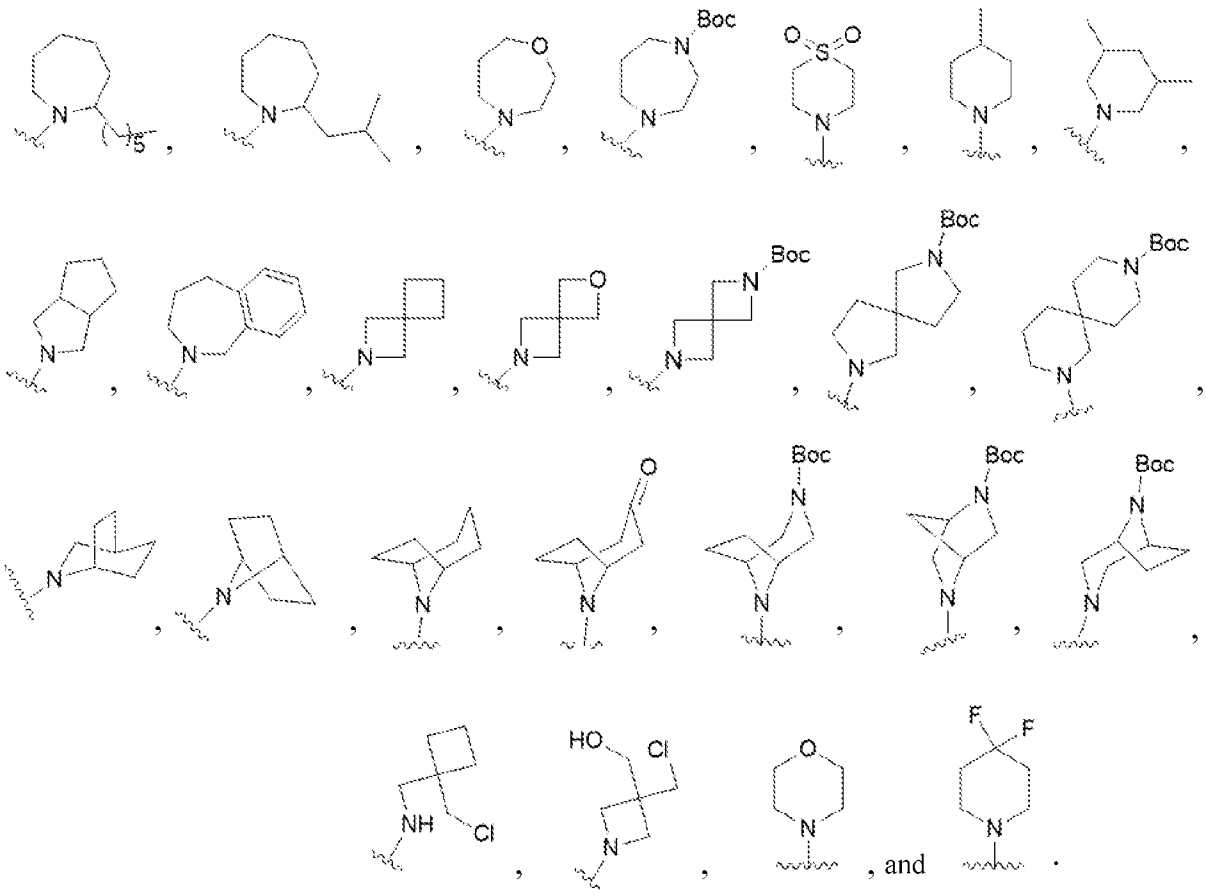
[098] In some embodiments, m is 1, 2, 3, 4, 5, or 6. In some embodiments, m is 4, 5, or 6. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3. In some embodiments, m is 4. In some embodiments, m is 5. In some embodiments, m is 6.

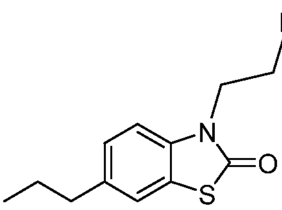
In some embodiments, R^{2A} is substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted

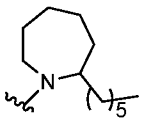
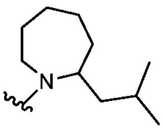
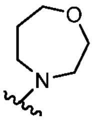
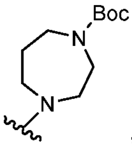
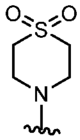
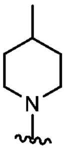
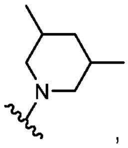
or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , and substituted or unsubstituted  ; wherein the substituted R^{2A} is substituted with one or more substituents independently selected from halo, C_{1-6} alkyl, -OH, -O(C_{1-6} alkyl), -NH_2, and -NMe_2.

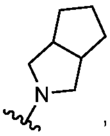
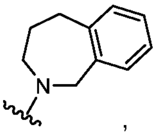
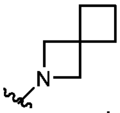
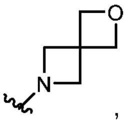
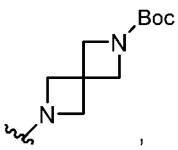
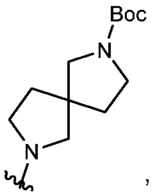
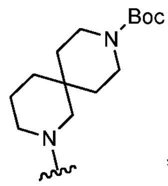
[099] In some embodiments, R^{2A} is unsubstituted. In some embodiments, R^{2A} is substituted. In some embodiments, R^{2A} is substituted with one or more substituents independently selected from halo, C_{1-6} alkyl, -OH, -O(C_{1-6} alkyl), -NH_2, and -NMe_2. In some embodiments, R^{2A} is substituted with halo or C_{1-6} alkyl. In some embodiments, R^{2A} is substituted with F, Cl, Br, methyl, ethyl, propyl, or isopropyl.

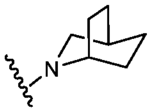
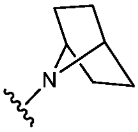
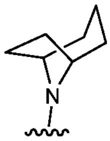
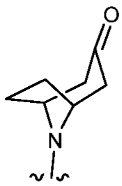
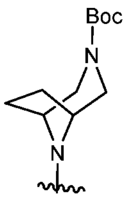
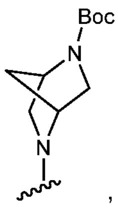
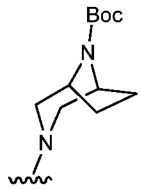
[0100] In some embodiments, R^{2A} is selected from the group consisting of:

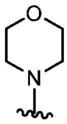
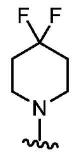


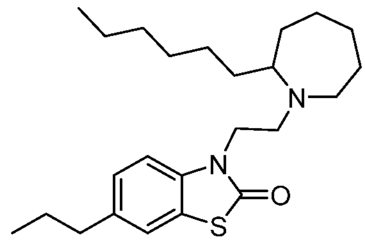
[0101] In some embodiments, the compound is of formula:  where R^{2A} is:

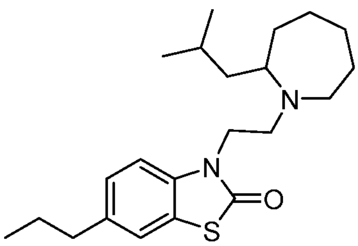
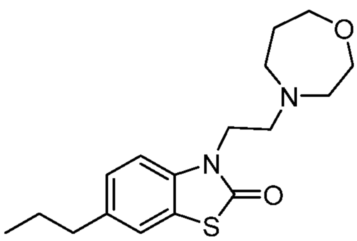
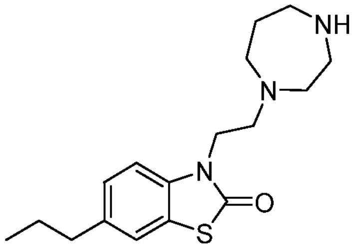
 ,  ,  ,  ,  ,  ,  ,

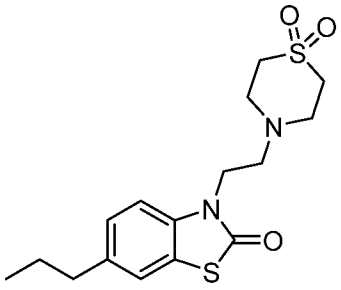
 ,  ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,  ,

 , or  .

[0102] In some embodiments, the compound is of formula:  ,

 ,  ,  ,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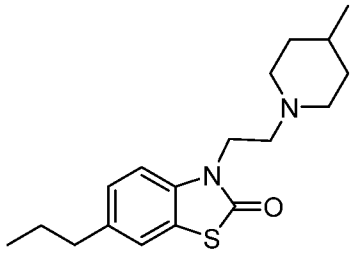
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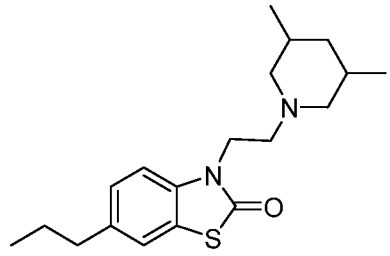
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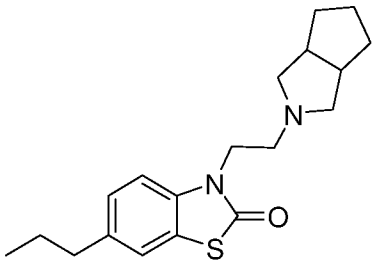
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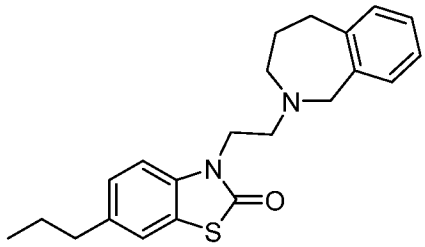
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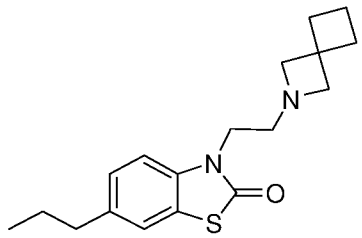
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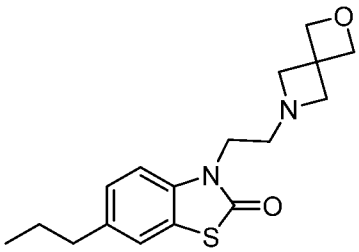
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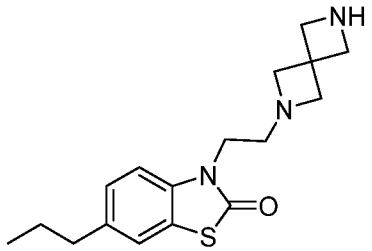
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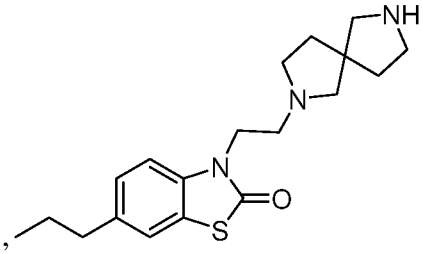
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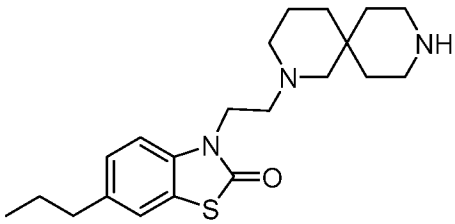
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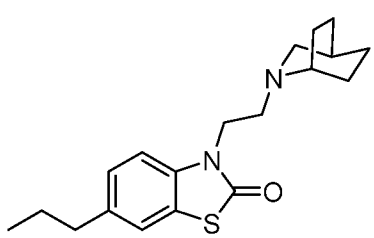
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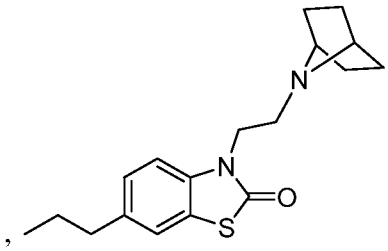
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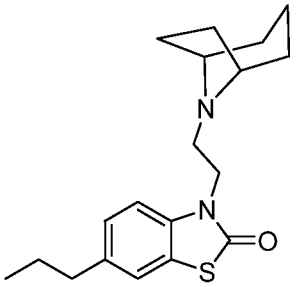
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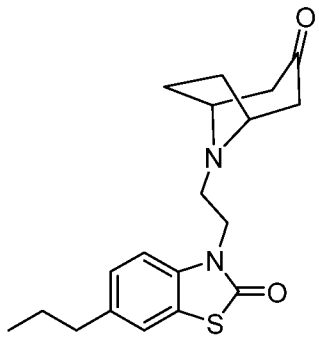
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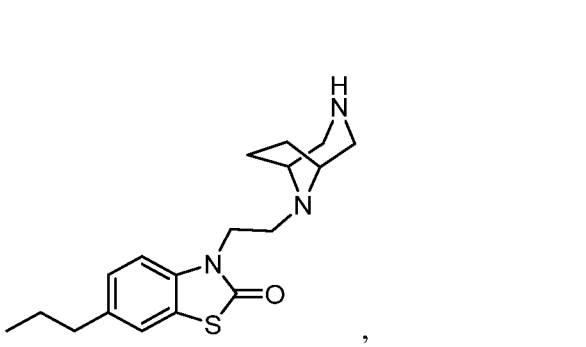
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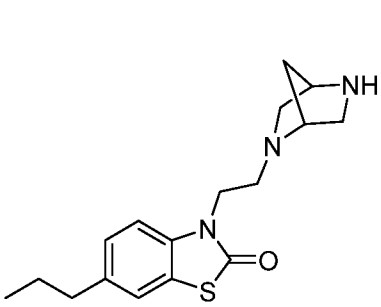
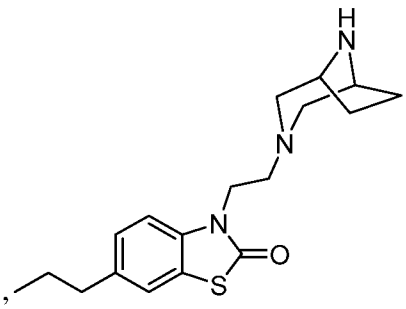
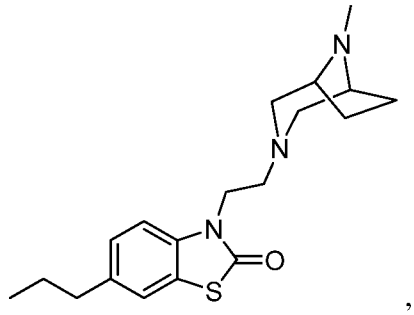
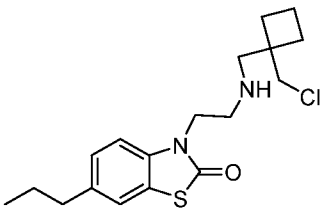
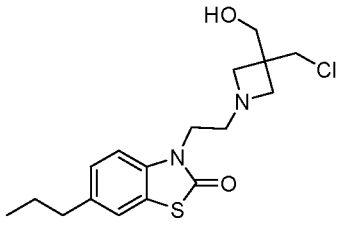
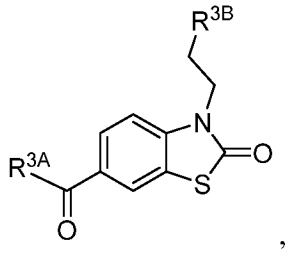






, or pharmaceutically acceptable salts thereof.

Compounds of Formula (II)

[0103] In one aspect, provided herein are compounds of Formula (II):



(II)

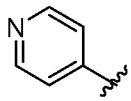
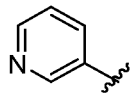
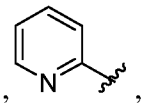
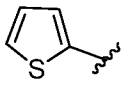
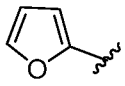
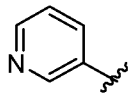
or pharmaceutically acceptable salt thereof, wherein:

R^{3A} is selected from the group consisting of unsubstituted or substituted pyridinyl, unsubstituted or substituted furanyl, and unsubstituted or substituted thiopheneyl; and

R^{3B} is selected from the group consisting of unsubstituted or substituted piperidinyl, unsubstituted or substituted morpholinyl, unsubstituted or substituted azepanyl, unsubstituted or substituted oxazepanyl, and unsubstituted or substituted 3,8-diazabicyclo[3.2.1]octanyl;

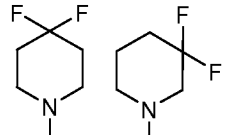
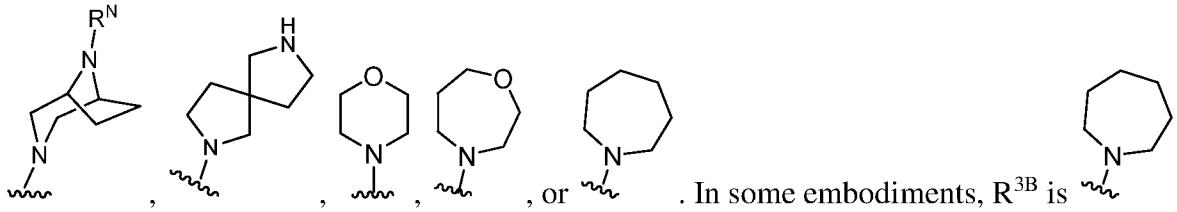
wherein the substituted R^{3A} and substituted R^{3B} are independently substituted with one or more substituents independently selected from halo, C_{1-6} alkyl, -OH, -O(C_{1-6} alkyl), -NH_2, and -NMe_2; and

wherein substituted R^{3B} is further optionally substituted with R^N, wherein R^N is H, C_{1-6} alkyl, or a nitrogen protecting group.

[0104] In some embodiments, R^{3A} is unsubstituted or substituted pyridinyl, unsubstituted or substituted furanyl, and unsubstituted or substituted thiopheneyl. In some embodiments, R^{3A} is unsubstituted or substituted pyridinyl. In some embodiments, R^{3A} is unsubstituted or substituted furanyl. In some embodiments, R^{3A} is unsubstituted or substituted thiopheneyl. In some embodiments, R^{3A} is substituted pyridinyl. In some embodiments, R^{3A} is substituted furanyl. In some embodiments, R^{3A} is substituted thiopheneyl. In some embodiments, R^{3A} is unsubstituted pyridinyl. In some embodiments, R^{3A} is unsubstituted furanyl. In some embodiments, R^{3A} is unsubstituted thiopheneyl. In some embodiments, R^{3A}  ,  ,  ,  , or  . In some embodiments, R^{3A} is  .

[0105] In some embodiments, R^{3A} is substituted with one or more substituents independently selected from halo, C_{1-6} alkyl, -OH, -O(C_{1-6} alkyl), $-NH_2$, and $-NMe_2$. In some embodiments, R^{3A} is substituted with one or more substituents independently selected from chloro, bromo, fluoro, methyl, ethyl, -OH, $-OCH_3$, $-NH_2$, and $-NMe_2$.

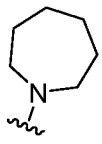
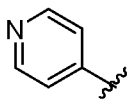
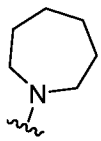
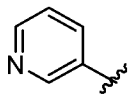
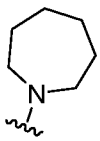
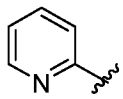
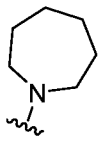
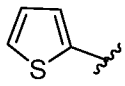
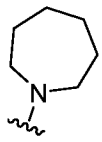
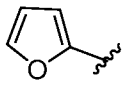
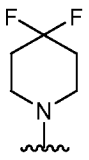
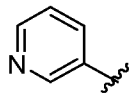
[0106] In some embodiments, R^{3B} is selected from the group consisting of unsubstituted or substituted piperidinyl, unsubstituted or substituted morpholinyl, unsubstituted or substituted azepanyl, unsubstituted or substituted oxazepanyl, and unsubstituted or substituted 3,8-diazabicyclo[3.2.1]octanyl. In some embodiments, R^{3B} is substituted piperidinyl. In some embodiments, R^{3B} is substituted morpholinyl. In some embodiments, R^{3B} is substituted azepanyl. In some embodiments, R^{3B} is substituted oxazepanyl. In some embodiments, R^{3B} is substituted 3,8-diazabicyclo[3.2.1]octanyl. In some embodiments, R^{3B} is unsubstituted piperidinyl. In some embodiments, R^{3B} is unsubstituted morpholinyl. In some embodiments, R^{3B} is unsubstituted azepanyl. In some embodiments, R^{3B} is unsubstituted oxazepanyl. In some embodiments, R^{3B} is

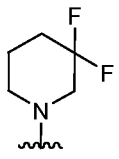
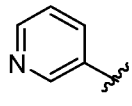
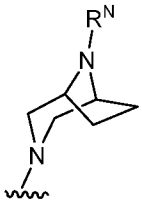
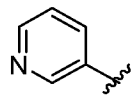
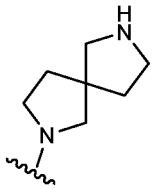
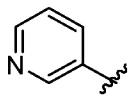
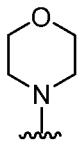
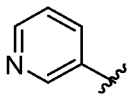
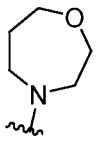
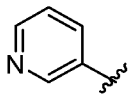
unsubstituted 3,8-diazabicyclo[3.2.1]octanyl. In some embodiments, R^{3B} is  ,  . In some embodiments, R^{3B} is .

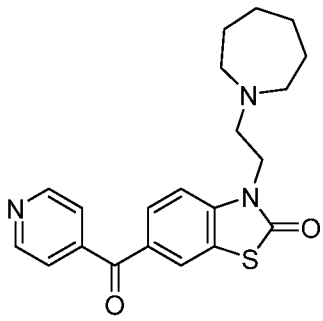
[0107] In some embodiments, R^{3B} is substituted with one or more substituents independently selected from halo, C_{1-6} alkyl, -OH, -O(C_{1-6} alkyl), -NH_2, and -NMe_2. In some embodiments, R^{3B} is substituted with one or more substituents independently selected from chloro, bromo, fluoro, methyl, ethyl, -OH, -OCH_3, -NH_2, and -NMe_2.

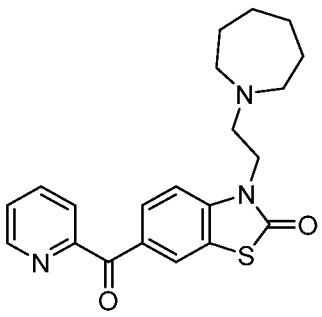
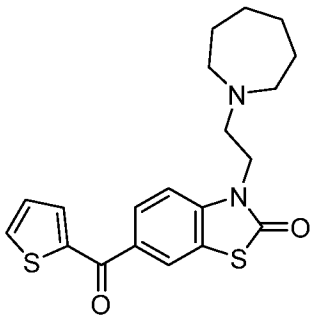
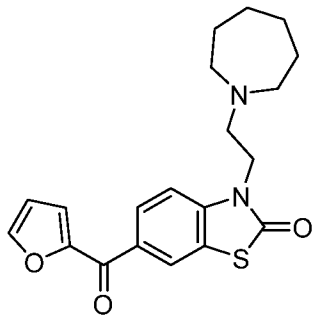
[0108] In some embodiments, R^{3B} is further optionally substituted with R^N, wherein R^N is H, C_{1-6} alkyl, or a nitrogen protecting group.

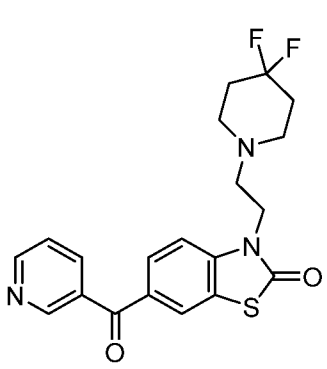
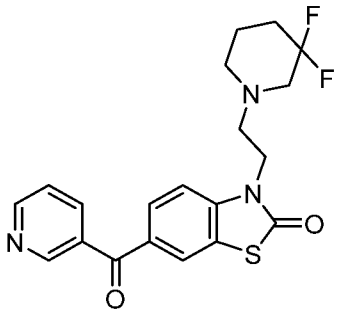
[0109] In some embodiments, R^N is H, C_{1-6} alkyl, or a nitrogen protecting group. In some embodiments, R^N is H, methyl, or Boc.

[0110] In some embodiments, R^{3B} is  and R^{3A} is  . In some embodiments,R^{3B} is  and R^{3A} is  . In some embodiments, R^{3B} is  and R^{3A} is  . In some embodiments, R^{3B} is  and R^{3A} is  . In some embodiments, R^{3B} is  and R^{3A} is  . In some embodiments, R^{3B} is  and R^{3A} is  . In some

embodiments, R^{3B} is  and R^{3A} is  . In some embodiments, R^{3B} is  and R^{3A} is  . In some embodiments, R^{3B} is  and R^{3A} is  . In some embodiments, R^{3B} is  and R^{3A} is  . In some embodiments, R^{3B} is  and R^{3A} is  .

[0111] In some embodiments, the compound of Formula (II) is:  ,

 ,  ,  ,


,

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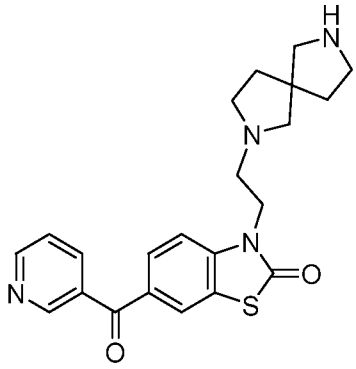
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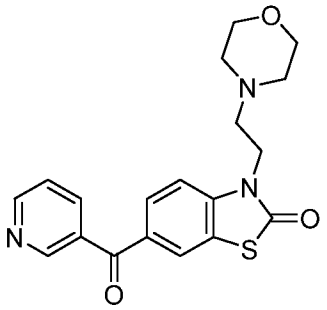
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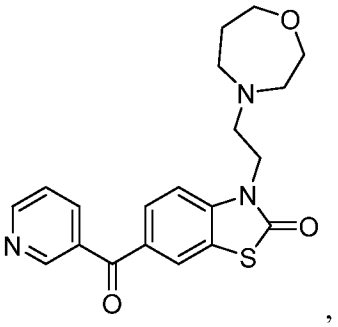
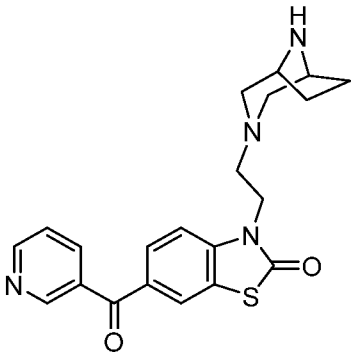
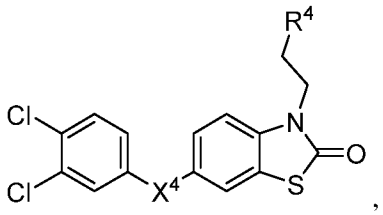

, or

, or

pharmaceutically acceptable salts thereof.

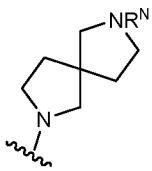
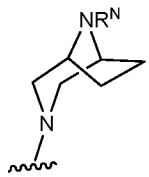
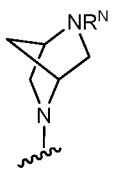
Compounds of Formula (III)

[0112] In one aspect, provided herein are compounds of Formula (III):


,

(III)

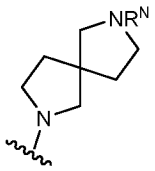
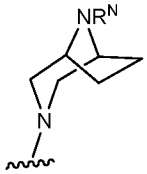
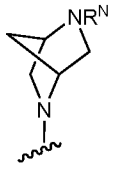
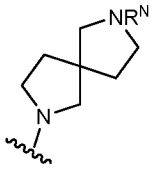
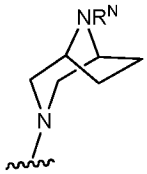
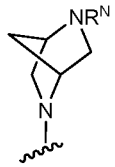
or pharmaceutically acceptable salt thereof, wherein:

R^4 is unsubstituted or substituted  , unsubstituted or substituted  , or unsubstituted or substituted  ;

wherein the substituted R^4 is substituted with one or more substituents independently selected from halo, C_{1-6} alkyl, -OH, -O(C_{1-6} alkyl), $-NH_2$, and $-NMe_2$;

R^N is H, C_{1-6} alkyl, or a nitrogen protecting group; and

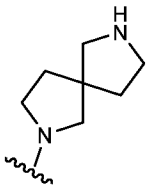
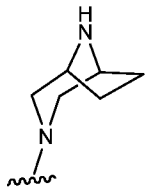
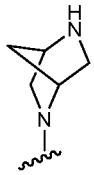
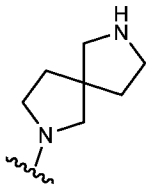
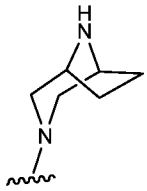
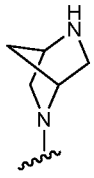
X^4 is $-CH_2-$ or -C(=O)-.

[0113] In some embodiments, R^4 is unsubstituted or substituted  , unsubstituted or substituted  , or unsubstituted or substituted  . In some embodiments, R^4 is unsubstituted or substituted  . In some embodiments, R^4 is unsubstituted or substituted  . In some embodiments, R^4 is unsubstituted or substituted  .

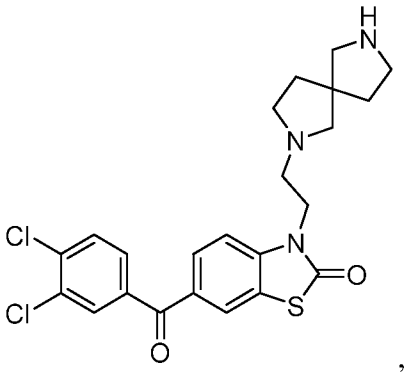
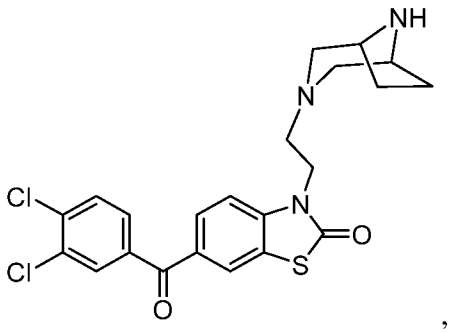
[0114] In some embodiments, R^4 is unsubstituted. In some embodiments, R^4 is substituted. In some embodiments, when R^4 is substituted, R^4 is substituted with one or more substituents independently selected from halo, C_{1-6} alkyl, -OH, -O(C_{1-6} alkyl), $-NH_2$, and $-NMe_2$. In some embodiments, the one or more substituents independently selected from chloro, bromo, fluoro, methyl, ethyl, -OH, $-OCH_3$, $-NH_2$, and $-NMe_2$.

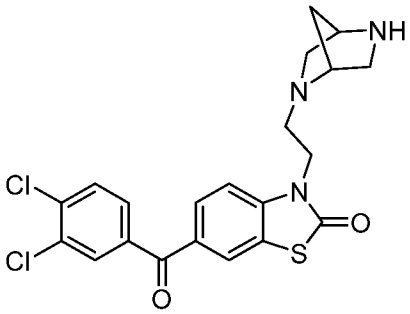
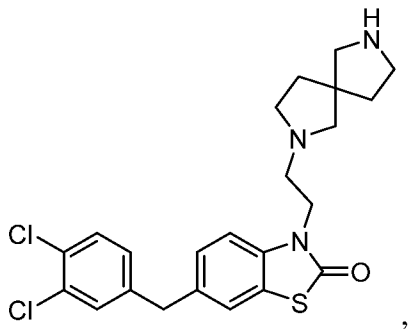
[0115] In some embodiments, R^N is H, C_{1-6} alkyl, or a nitrogen protecting group. In some embodiments, R^N is H. In some embodiments, R^N is C_{1-6} alkyl. In some embodiments, R^N is a nitrogen protecting group. In some embodiments, R^N is H, methyl, or Boc.

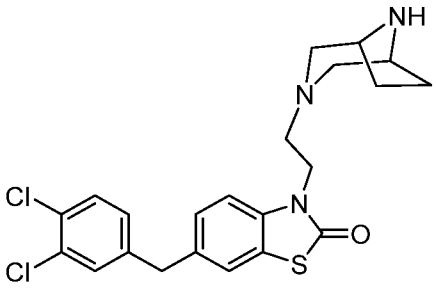
[0116] In some embodiments, X^4 is $-CH_2-$ or -C(=O)-. In some embodiments, X^4 is $-CH_2-$. In some embodiments, X^4 is -C(=O)-.

[0117] In some embodiments, R^4 is  and X^4 is -CH_2-. In some embodiments, R^4 is  and X^4 is -CH_2-. In some embodiments, R^4 is  and X^4 is -CH_2-. In some embodiments, R^4 is  and X^4 is -C(=O)-. In some embodiments, R^4 is  and X^4 is -C(=O)-. In some embodiments, R^4 is  and X^4 is -C(=O)-.

[0118] In some embodiments, the compound of formula (III) is of formula:

 ,  ,

 ,  ,



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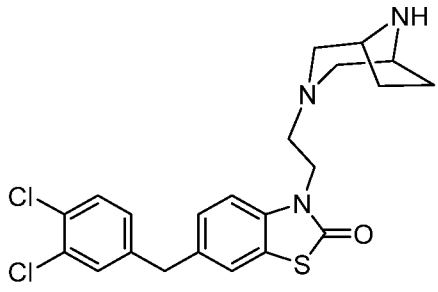
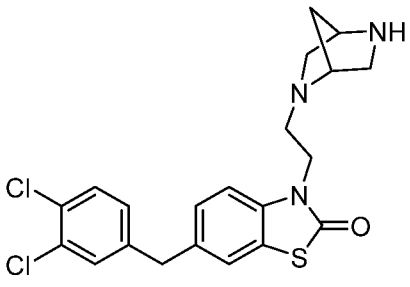


, or



, or pharmaceutically acceptable salts thereof.

Compositions, Administration, and Kits

[0119] The present disclosure provides pharmaceutical compositions comprising a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition described herein comprises a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0120] In certain embodiments, the compound described herein is provided in an effective amount in the pharmaceutical composition. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is a prophylactically effective amount. In certain embodiments, the effective amount is an amount effective for treating a proliferative disease in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for preventing a proliferative disease in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for treating a hematological disease in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for preventing a hematological disease in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for treating a neurological disease in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for preventing a neurological disease in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for treating a in a painful condition

subject in need thereof. In certain embodiments, the effective amount is an amount effective for preventing a painful condition in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for treating a psychiatric disorder in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for preventing a psychiatric disorder in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for treating a metabolic disorder in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for preventing a metabolic disorder in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for reducing the risk of developing a disease (*e.g.*, proliferative disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for inhibiting the activity (*e.g.*, aberrant activity, such as increased activity) of a protein kinase in a subject or cell.

[0121] In certain embodiments, the subject is an animal. The animal may be of either sex and may be at any stage of development. In certain embodiments, the subject described herein is a human. In certain embodiments, the subject is a non-human animal. In certain embodiments, the subject is a mammal. In certain embodiments, the subject is a non-human mammal. In certain embodiments, the subject is a domesticated animal, such as a dog, cat, cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a companion animal, such as a dog or cat. In certain embodiments, the subject is a livestock animal, such as a cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a zoo animal. In another embodiment, the subject is a research animal, such as a rodent (*e.g.*, mouse, rat), dog, pig, or non-human primate. In certain embodiments, the animal is a genetically engineered animal. In certain embodiments, the animal is a transgenic animal (*e.g.*, transgenic mice and transgenic pigs). In certain embodiments, the subject is a fish or reptile.

[0122] In certain embodiments, the cell is present *in vitro*. In certain embodiments, the cell is present *in vivo*.

[0123] In certain embodiments, the effective amount is an amount effective for inhibiting the activity of a protein by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, or at least about 98%. In certain embodiments, the effective amount is an amount effective for inhibiting the activity of a sigma receptor by not more than

10%, not more than 20%, not more than 30%, not more than 40%, not more than 50%, not more than 60%, not more than 70%, not more than 80%, not more than 90%, not more than 95%, or not more than 98%. In certain embodiments, the effective amount is an amount effective for inhibiting the activity of a sigma receptor by a range between a percentage described in this paragraph and another percentage described in this paragraph, inclusive.

[0124] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmaceutics. In general, such preparatory methods include bringing the compound described herein (*i.e.*, the "active ingredient") into association with a carrier or excipient, and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping, and/or packaging the product into a desired single- or multi-dose unit.

[0125] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. A "unit dose" is a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage, such as one-half or one-third of such a dosage.

[0126] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition described herein will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. The composition may comprise between 0.1% and 100% (w/w) active ingredient.

[0127] Pharmaceutically acceptable excipients used in the manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and perfuming agents may also be present in the composition.

[0128] Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, and mixtures thereof.

[0129] Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose, and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, and mixtures thereof.

[0130] Exemplary surface active agents and/or emulsifiers include natural emulsifiers (*e.g.*, acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (*e.g.*, bentonite (aluminum silicate) and Veegum (magnesium aluminum silicate)), long chain amino acid derivatives, high molecular weight alcohols (*e.g.*, stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (*e.g.*, carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (*e.g.*, carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (*e.g.*, polyoxyethylene sorbitan monolaurate (Tween® 20), polyoxyethylene sorbitan (Tween® 60), polyoxyethylene sorbitan monooleate (Tween® 80), sorbitan monopalmitate (Span® 40), sorbitan monostearate (Span® 60), sorbitan tristearate (Span® 65), glyceryl monooleate, sorbitan monooleate (Span® 80), polyoxyethylene esters (*e.g.*, polyoxyethylene monostearate (Myrj® 45), polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol®), sucrose fatty acid esters, polyethylene glycol fatty acid esters (*e.g.*, Cremophor®), polyoxyethylene ethers, (*e.g.*, polyoxyethylene lauryl ether (Brij® 30)), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic® F-68, poloxamer P-188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, and/or mixtures thereof.

[0131] Exemplary binding agents include starch (*e.g.*, cornstarch and starch paste), gelatin, sugars (*e.g.*, sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, *etc.*), natural and synthetic gums (*e.g.*, acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (Veegum®), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, and/or mixtures thereof.

[0132] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, antiprotozoan preservatives, alcohol preservatives, acidic preservatives, and other preservatives. In certain embodiments, the preservative is an antioxidant. In other embodiments, the preservative is a chelating agent.

[0133] Exemplary antioxidants include alpha tocopherol, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

[0134] Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (*e.g.*, sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof (*e.g.*, citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof. Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal.

[0135] Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

[0136] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

[0137] Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid.

[0138] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant® Plus, Phenonip®, methylparaben, Germall® 115, Germaben® II, Neolone®, Kathon®, and Euxyl®.

[0139] Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, and mixtures thereof.

[0140] Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof.

[0141] Exemplary natural oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana,

savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary synthetic oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and mixtures thereof.

[0142] Liquid dosage forms for oral and parenteral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredients, the liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (*e.g.*, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, the conjugates described herein are mixed with solubilizing agents such as Cremophor®, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and mixtures thereof.

[0143] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can be a sterile injectable solution, suspension, or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, U.S.P., and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed including synthetic mono- or di-glycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0144] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0145] In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form may be accomplished by dissolving or suspending the drug in an oil vehicle.

[0146] Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing the conjugates described herein with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol, or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active ingredient.

[0147] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active ingredient is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or (a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, (c) humectants such as glycerol, (d) disintegrating agents such as agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, (e) solution retarding agents such as paraffin, (f) absorption accelerators such as quaternary ammonium compounds, (g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, (h) absorbents such as kaolin and bentonite clay, and (i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets, and pills, the dosage form may include a buffering agent.

[0148] Solid compositions of a similar type can be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the art of pharmacology. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of encapsulating

compositions which can be used include polymers and waxes. Solid compositions of a similar type can be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[0149] The active ingredient can be in a micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings, and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active ingredient can be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may comprise, as is normal practice, additional components other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may comprise buffering agents. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of encapsulating agents which can be used include polymers and waxes.

[0150] Dosage forms for topical and/or transdermal administration of a compound described herein may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, and/or patches. Generally, the active ingredient is admixed under sterile conditions with a pharmaceutically acceptable carrier or excipient and/or any needed preservatives and/or buffers as can be required. Additionally, the present disclosure contemplates the use of transdermal patches, which often have the added advantage of providing controlled delivery of an active ingredient to the body. Such dosage forms can be prepared, for example, by dissolving and/or dispensing the active ingredient in the proper medium. Alternatively or additionally, the rate can be controlled by either providing a rate controlling membrane and/or by dispersing the active ingredient in a polymer matrix and/or gel.

[0151] Suitable devices for use in delivering intradermal pharmaceutical compositions described herein include short needle devices. Intradermal compositions can be administered by devices which limit the effective penetration length of a needle into the skin. Alternatively or additionally, conventional syringes can be used in the classical mantoux method of intradermal administration. Jet injection devices which deliver liquid formulations to the dermis *via* a liquid jet injector and/or *via* a needle which pierces the stratum corneum and produces a jet which

reaches the dermis are suitable. Ballistic powder/particle delivery devices which use compressed gas to accelerate the compound in powder form through the outer layers of the skin to the dermis are suitable.

[0152] Formulations suitable for topical administration include, but are not limited to, liquid and/or semi-liquid preparations such as liniments, lotions, oil-in-water and/or water-in-oil emulsions such as creams, ointments, and/or pastes, and/or solutions and/or suspensions. Topically administrable formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of the active ingredient can be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

[0153] A pharmaceutical composition described herein can be prepared, packaged, and/or sold in a formulation suitable for pulmonary administration *via* the buccal cavity. Such a formulation may comprise dry particles which comprise the active ingredient and which have a diameter in the range from about 0.5 to about 7 nanometers, or from about 1 to about 6 nanometers. Such compositions are conveniently in the form of dry powders for administration using a device comprising a dry powder reservoir to which a stream of propellant can be directed to disperse the powder and/or using a self-propelling solvent/powder dispensing container such as a device comprising the active ingredient dissolved and/or suspended in a low-boiling propellant in a sealed container. Such powders comprise particles wherein at least 98% of the particles by weight have a diameter greater than 0.5 nanometers and at least 95% of the particles by number have a diameter less than 7 nanometers. Alternatively, at least 95% of the particles by weight have a diameter greater than 1 nanometer and at least 90% of the particles by number have a diameter less than 6 nanometers. Dry powder compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

[0154] Low boiling propellants generally include liquid propellants having a boiling point of below 65 °F at atmospheric pressure. Generally the propellant may constitute 50 to 99.9% (w/w) of the composition, and the active ingredient may constitute 0.1 to 20% (w/w) of the composition. The propellant may further comprise additional ingredients such as a liquid non-ionic and/or solid anionic surfactant and/or a solid diluent (which may have a particle size of the same order as particles comprising the active ingredient).

[0155] Pharmaceutical compositions described herein formulated for pulmonary delivery may provide the active ingredient in the form of droplets of a solution and/or suspension. Such formulations can be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, comprising the active ingredient, and may conveniently be administered using any nebulization and/or atomization device. Such formulations may further comprise one or more additional ingredients including, but not limited to, a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, and/or a preservative such as methylhydroxybenzoate. The droplets provided by this route of administration may have an average diameter in the range from about 0.1 to about 200 nanometers.

[0156] Formulations described herein as being useful for pulmonary delivery are useful for intranasal delivery of a pharmaceutical composition described herein. Another formulation suitable for intranasal administration is a coarse powder comprising the active ingredient and having an average particle from about 0.2 to 500 micrometers. Such a formulation is administered by rapid inhalation through the nasal passage from a container of the powder held close to the nares.

[0157] Formulations for nasal administration may, for example, comprise from about as little as 0.1% (w/w) to as much as 100% (w/w) of the active ingredient, and may comprise one or more of the additional ingredients described herein. A pharmaceutical composition described herein can be prepared, packaged, and/or sold in a formulation for buccal administration. Such formulations may, for example, be in the form of tablets and/or lozenges made using conventional methods, and may contain, for example, 0.1 to 20% (w/w) active ingredient, the balance comprising an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations for buccal administration may comprise a powder and/or an aerosolized and/or atomized solution and/or suspension comprising the active ingredient. Such powdered, aerosolized, and/or aerosolized formulations, when dispersed, may have an average particle and/or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one or more of the additional ingredients described herein.

[0158] A pharmaceutical composition described herein can be prepared, packaged, and/or sold in a formulation for ophthalmic administration. Such formulations may, for example, be in the form of eye drops including, for example, a 0.1-1.0% (w/w) solution and/or suspension of the active

ingredient in an aqueous or oily liquid carrier or excipient. Such drops may further comprise buffering agents, salts, and/or one or more other of the additional ingredients described herein. Other ophthalmically-administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form and/or in a liposomal preparation. Ear drops and/or eye drops are also contemplated as being within the scope of this disclosure.

[0159] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation.

[0160] Compounds provided herein are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions described herein will be decided by a physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex, and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

[0161] The compounds and compositions provided herein can be administered by any route, including enteral (*e.g.*, oral), parenteral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, interdermal, rectal, intravaginal, intraperitoneal, topical (as by powders, ointments, creams, and/or drops), mucosal, nasal, bucal, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; and/or as an oral spray, nasal spray, and/or aerosol. Specifically contemplated routes are oral administration, intravenous administration (*e.g.*, systemic intravenous injection), regional administration *via* blood and/or lymph supply, and/or direct administration to an affected site. In general, the most appropriate route of administration will depend upon a variety of factors including the nature of

the agent (*e.g.*, its stability in the environment of the gastrointestinal tract), and/or the condition of the subject (*e.g.*, whether the subject is able to tolerate oral administration). In certain embodiments, the compound or pharmaceutical composition described herein is suitable for topical administration to the eye of a subject.

[0162] The exact amount of a compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound, mode of administration, and the like. An effective amount may be included in a single dose (*e.g.*, single oral dose) or multiple doses (*e.g.*, multiple oral doses). In certain embodiments, when multiple doses are administered to a subject or applied to a tissue or cell, any two doses of the multiple doses include different or substantially the same amounts of a compound described herein. In certain embodiments, when multiple doses are administered to a subject or applied to a tissue or cell, the frequency of administering the multiple doses to the subject or applying the multiple doses to the tissue or cell is three doses a day, two doses a day, one dose a day, one dose every other day, one dose every third day, one dose every week, one dose every two weeks, one dose every three weeks, or one dose every four weeks. In certain embodiments, the frequency of administering the multiple doses to the subject or applying the multiple doses to the tissue or cell is one dose per day. In certain embodiments, the frequency of administering the multiple doses to the subject or applying the multiple doses to the tissue or cell is two doses per day. In certain embodiments, the frequency of administering the multiple doses to the subject or applying the multiple doses to the tissue or cell is three doses per day. In certain embodiments, when multiple doses are administered to a subject or applied to a tissue or cell, the duration between the first dose and last dose of the multiple doses is one day, two days, four days, one week, two weeks, three weeks, one month, two months, three months, four months, six months, nine months, one year, two years, three years, four years, five years, seven years, ten years, fifteen years, twenty years, or the lifetime of the subject, tissue, or cell. In certain embodiments, the duration between the first dose and last dose of the multiple doses is three months, six months, or one year. In certain embodiments, the duration between the first dose and last dose of the multiple doses is the lifetime of the subject, tissue, or cell. In certain embodiments, a dose (*e.g.*, a single dose, or any dose of multiple doses) described herein includes independently between 0.1 μg and 1 μg, between 0.001 mg and 0.01 mg, between 0.01 mg and 0.1 mg, between 0.1 mg and 1 mg,

between 1 mg and 3 mg, between 3 mg and 10 mg, between 10 mg and 30 mg, between 30 mg and 100 mg, between 100 mg and 300 mg, between 300 mg and 1,000 mg, or between 1 g and 10 g, inclusive, of a compound described herein. In certain embodiments, a dose described herein includes independently between 1 mg and 3 mg, inclusive, of a compound described herein. In certain embodiments, a dose described herein includes independently between 3 mg and 10 mg, inclusive, of a compound described herein. In certain embodiments, a dose described herein includes independently between 10 mg and 30 mg, inclusive, of a compound described herein. In certain embodiments, a dose described herein includes independently between 30 mg and 100 mg, inclusive, of a compound described herein.

[0163] Dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

[0164] A compound or composition, as described herein, can be administered in combination with one or more additional pharmaceutical agents (*e.g.*, therapeutically and/or prophylactically active agents). The compounds or compositions can be administered in combination with additional pharmaceutical agents that improve their activity (*e.g.*, activity (*e.g.*, potency and/or efficacy) in treating a disease in a subject in need thereof, in preventing a disease in a subject in need thereof, in reducing the risk to develop a disease in a subject in need thereof, and/or in inhibiting the activity of a protein kinase in a subject or cell), improve bioavailability, improve safety, reduce drug resistance, reduce and/or modify metabolism, inhibit excretion, and/or modify distribution in a subject or cell. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects. In certain embodiments, a pharmaceutical composition described herein including a compound described herein and an additional pharmaceutical agent shows a synergistic effect that is absent in a pharmaceutical composition including one of the compound and the additional pharmaceutical agent, but not both. In some embodiments, the additional pharmaceutical agent achieves a desired effect for the same disorder. In some embodiments, the additional pharmaceutical agent achieves different effects.

[0165] The compound or composition can be administered concurrently with, prior to, or subsequent to one or more additional pharmaceutical agents, which may be useful as, *e.g.*,

combination therapies. Pharmaceutical agents include therapeutically active agents. Pharmaceutical agents also include prophylactically active agents. Pharmaceutical agents include small organic molecules such as drug compounds (*e.g.*, compounds approved for human or veterinary use by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins, and cells. In certain embodiments, the additional pharmaceutical agent is a pharmaceutical agent useful for treating and/or preventing a disease (*e.g.*, proliferative disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder). Each additional pharmaceutical agent may be administered at a dose and/or on a time schedule determined for that pharmaceutical agent. The additional pharmaceutical agents may also be administered together with each other and/or with the compound or composition described herein in a single dose or composition or administered separately in different doses or compositions. The particular combination to employ in a regimen will take into account compatibility of the compound described herein with the additional pharmaceutical agent(s) and/or the desired therapeutic and/or prophylactic effect to be achieved. In general, it is expected that the additional pharmaceutical agent(s) in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

[0166] The additional pharmaceutical agents include, but are not limited to, anti-proliferative agents, anti-cancer agents, anti-angiogenesis agents, steroidal or non-steroidal anti-inflammatory agents, immunosuppressants, anti-bacterial agents, anti-viral agents, cardiovascular agents, cholesterol-lowering agents, anti-diabetic agents, anti-allergic agents, contraceptive agents, pain-relieving agents, anesthetics, anti–coagulants, inhibitors of an enzyme, steroidal agents, steroidal or antihistamine, antigens, vaccines, antibodies, decongestant, sedatives, opioids, analgesics, anti–pyretics, hormones, and prostaglandins. In certain embodiments, the additional pharmaceutical agent is an anti-proliferative agent. In certain embodiments, the additional pharmaceutical agent is an anti-cancer agent. In certain embodiments, the additional pharmaceutical agent is an anti-viral agent. In certain embodiments, the additional

pharmaceutical agent is an binder or inhibitor of a protein kinase. In certain embodiments, the additional pharmaceutical agent is selected from the group consisting of epigenetic or transcriptional modulators (*e.g.*, DNA methyltransferase inhibitors, histone deacetylase inhibitors (HDAC inhibitors), lysine methyltransferase inhibitors), antimitotic drugs (*e.g.*, taxanes and vinca alkaloids), hormone receptor modulators (*e.g.*, estrogen receptor modulators and androgen receptor modulators), cell signaling pathway inhibitors (*e.g.*, tyrosine protein kinase inhibitors), modulators of protein stability (*e.g.*, proteasome inhibitors), Hsp90 inhibitors, glucocorticoids, all-*trans* retinoic acids, and other agents that promote differentiation. In certain embodiments, the compounds described herein or pharmaceutical compositions can be administered in combination with an anti-cancer therapy including, but not limited to, surgery, radiation therapy, transplantation (*e.g.*, stem cell transplantation, bone marrow transplantation), immunotherapy, and chemotherapy. Additional pharmaceutical agents include small organic molecules such as drug compounds (*e.g.*, compounds approved by the US Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins and cells.

[0167] The present disclosure also provides a kit comprising: a compound provided herein (*e.g.*, a compound of Formula (I), (II), or (III)), or pharmaceutically acceptable salt thereof, or a composition provided herein (*e.g.*, a composition comprising a compound of Formula (I), (II), or (III)); and instructions for administering the compound, or pharmaceutically acceptable salt thereof, or composition to a subject.

[0168] Also encompassed by the disclosure are kits (*e.g.*, pharmaceutical packs). The kits provided may comprise a pharmaceutical composition or compound described herein and a container (*e.g.*, a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of a pharmaceutical composition or compound described herein. In some embodiments, the pharmaceutical composition or compound described herein provided in the first container and the second container are combined to form one unit dosage form.

[0169] Thus, in one aspect, provided are kits including a first container comprising a compound or pharmaceutical composition described herein. In certain embodiments, the kits are useful for treating a disease (*e.g.*, proliferative disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof. In certain embodiments, the kits are useful for preventing a disease (*e.g.*, proliferative disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof. In certain embodiments, the kits are useful for reducing the risk of developing a disease (*e.g.*, proliferative disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof. In certain embodiments, the kits are useful for inhibiting the activity (*e.g.*, aberrant activity, such as increased activity) of a protein kinase in a subject or cell.

[0170] In certain embodiments, a kit described herein further includes instructions for using the kit. A kit described herein may also include information as required by a regulatory agency such as the U.S. Food and Drug Administration (FDA). In certain embodiments, the information included in the kits is prescribing information. In certain embodiments, the kits and instructions provide for treating a disease (*e.g.*, proliferative disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof. In certain embodiments, the kits and instructions provide for preventing a disease (*e.g.*, proliferative disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof. In certain embodiments, the kits and instructions provide for reducing the risk of developing a disease (*e.g.*, proliferative disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof. In certain embodiments, the kits and instructions provide for inhibiting the activity (*e.g.*, aberrant activity, such as increased activity) of a protein kinase in a subject or cell. A kit described herein may include one or more additional pharmaceutical agents described herein as a separate composition.

Methods

[0171] Provided herein are methods utilizing and uses of the compounds disclosed herein (*e.g.*, compounds of Formula (I), (II), and (III)).

[0172] In an additional aspect, the present disclosure provides methods of treating or preventing substance intake by a subject comprising administering to the subject a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Formula (I), (II), or (III)), or pharmaceutically acceptable salt thereof, or a composition provided herein (*e.g.*, a composition comprising a compound of Formula (I), (II), or (III)). In some embodiments, the substance is cocaine or methamphetamine. In certain embodiments, the substance is cocaine. In certain embodiments, the substance is methamphetamine.

[0173] In another aspect, provided herein are methods of treating or preventing substance use disorder in a subject comprising administering to the subject a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Formula (I), (II), or (III)), or pharmaceutically acceptable salt thereof, or a composition provided herein (*e.g.*, a composition comprising a compound of Formula (I), (II), or (III)). In some embodiments, the substance is cocaine or methamphetamine. In certain embodiments, the substance is cocaine. In certain embodiments, the substance is methamphetamine.

[0174] In one aspect, the present disclosure provides methods of treating the symptoms of substance use disorder in a subject comprising administering to the subject a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Formula (I), (II), or (III)), or pharmaceutically acceptable salt thereof, or a composition provided herein (*e.g.*, a composition comprising a compound of Formula (I), (II), or (III)). In some embodiments, the substance is cocaine or methamphetamine. In certain embodiments, the substance is cocaine. In certain embodiments, the substance is methamphetamine.

[0175] In an additional aspect, the present disclosure provides methods of treating or preventing substance addiction in a subject comprising administering to the subject a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Formula (I), (II), or (III)), or pharmaceutically acceptable salt thereof, or a composition provided herein (*e.g.*, a composition comprising a compound of Formula (I), (II), or (III)). In some embodiments, the substance is cocaine or methamphetamine. In certain embodiments, the substance is cocaine. In certain embodiments, the substance is methamphetamine.

[0176] In another aspects, provided herein are methods of treating the symptoms of substance addiction in a subject comprising administering to the subject a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Formula (I), (II), or (III)), or

pharmaceutically acceptable salt thereof, or a composition provided herein (*e.g.*, a composition comprising a compound of Formula (I), (II), or (III)). In some embodiments, the substance is cocaine or methamphetamine. In certain embodiments, the substance is cocaine. In certain embodiments, the substance is methamphetamine.

[0177] In one aspect, the present disclosure provides methods of treating or preventing neurotoxic effects resulting from substance use disorder, substance addiction, and/or substance intake by a subject comprising administering to the subject a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Formula (I), (II), or (III)), or pharmaceutically acceptable salt thereof, or a composition provided herein (*e.g.*, a composition comprising a compound of Formula (I), (II), or (III)). In some embodiments, the substance is cocaine or methamphetamine. In certain embodiments, the substance is cocaine. In certain embodiments, the substance is methamphetamine.

[0178] In a further aspect, provided herein are methods of treating or preventing a disease or disorder associated with one or more sigma receptors comprising administering to a subject a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Formula (I), (II), or (III)), or pharmaceutically acceptable salt thereof, or a composition provided herein (*e.g.*, a composition comprising a compound of Formula (I), (II), or (III)). In some embodiments, the disease or disorder is a neurological disease, a proliferative disease, a painful condition, or a psychiatric disorder. In some embodiments, the disease or disorder is pain, a neurodegenerative disorder (*e.g.*, Alzheimer's disease, Parkinson's disease), substance addiction, cancer, depression, schizophrenia, anxiety, stroke, obsessive compulsive disorder, or multiple sclerosis.

[0179] Another object of the present disclosure is the use of a compound as described herein (*e.g.*, a compound of Formula (I), (II), or (III)), or pharmaceutically acceptable salt thereof, or a composition provided herein (*e.g.*, a composition comprising a compound of Formula (I), (II), or (III)) in the manufacture of a medicament for use in the treatment of a disorder or disease described herein. Another object of the present disclosure is the use of a compound as described herein (*e.g.*, a compound of Formula (I), (II), or (III)), or pharmaceutically acceptable salt thereof, or a composition provided herein (*e.g.*, a composition comprising a compound of Formula (I), (II), or (III)) for use in the treatment of a disorder or disease described herein. Another object of the present disclosure is the use of a compound as described herein (*e.g.*, a compound of Formula (I), (II), or (III)), or pharmaceutically acceptable salt thereof, or a

composition provided herein (*e.g.*, a composition comprising a compound of Formula (I), (II), or (III)) in the manufacture of a veterinary composition for use in the treatment or prevention of a disorder or disease in veterinary applications.

[0180] Another object of the invention is a method for making a compound as described herein (*e.g.*, a compound of Formula (I), (II), or (III)), or pharmaceutically acceptable salt thereof, the method comprising one or more reactions of chemical transformations using compounds (*e.g.*, starting compounds, intermediate compounds, reagent compounds, protected compounds, etc.) and reaction conditions as described herein. The method can comprise a single chemical reaction or a sequence of multiple chemical reactions. The method can include isolation or purification of each reaction product, then subjecting the resulting product to further chemical transformation to the desired final product. Alternatively, a reaction product may be carried on without isolation or purification of the reaction product (*i.e.*, *in situ*) whereupon such reaction product is further reacted by treatment with one or more reagents under appropriate conditions to form the next resulting product.

EXAMPLES

[0181] In order that the present disclosure may be more fully understood, the following examples are set forth. The synthetic and biological examples described in this Application are offered to illustrate the compounds, pharmaceutical compositions, methods, and uses provided herein and are not to be construed in any way as limiting their scope.

General Procedures

[0182] ***In Vitro* Metabolic Stability.** *In vitro* metabolic stability of novel compounds was assessed in rat liver microsomes (RLMs). Liver microsome-based assays were performed to rank order/evaluate compounds for their metabolic stability. *In vitro* metabolism was performed by incubating a desired concentration (1 μM) of test compound and microsomal proteins (1 mg/mL protein concentration) in phosphate buffer (50 mM, pH 7.4), supplemented with or without NADPH in a bench-top shaker for 30 min at 37 ± 0.5 °C. Verapamil was used as a positive control while the metabolic reaction without NADPH was used as a negative control. The reaction was initiated by the addition of NADPH (1 mM) into pre-incubated reaction mixture. *A*liquots (25 μL) were withdrawn at various time points (0, 5, 10, 15, 20, and 30 min) and the

reaction was quenched with 125 µL of ice-cold acetonitrile with internal standard, phenacetin. These samples were then filtered through 0.45 µm using membrane filtration 96 well plate under centrifugation at 2000 x g for 10 min. The filtrate was injected on to LC-MS/MS system.

Binding assays for the σ_1R and σ_2R

[0183] ***Rat Brain Membrane Protein Preparation.*** Sigma receptor binding studies were conducted with rat brain membranes in Dr. Toll's laboratory as previously described (Berzetei-Gurske & Toll, 1992; Mésangeau et al., 2008 & 2011; Bhat et al., 2013). Crude P2 membranes were prepared from rat brain. Earlier studies confirmed that there is significant homology and identity between the sequence of the targeted receptors and transporters between rats and mice, and direct comparisons of sigma receptor binding in the brains of the two species were comparable (Sircar et al., 1986). With this in mind, Dr. Toll used rat brain tissue where he obtained approximately ten times more brain tissue as compared to mice, thereby greatly reducing the number of animals needed for these studies. Seventeen mL of sucrose buffer was added to intact rat brain before homogenization in a Polytron homogenizer. The homogenate was spun at 17,000 x g for 10 minutes at 4 °C. The supernatant was then transferred to another tube and spun at 50000 x g for 2 hours at 4 °C. The supernatant was discarded and 5 mL of Tris buffer with pH of 8.0 is added to final pellet, which was then homogenized. The protein was quantified using the established methods (Bradford, 1976) and then aliquoted to Eppendorf vials and stored at a temperature of -80 °C.

[0184] ***Sigma Binding to Rat Brain Membranes with the Radioligand Competition Binding Assay.*** Test ligands (13 concentrations, 0.001-1,000 nM) were incubated for 120 min at 25°C in 50 mM Tris-HCl, pH 8.0 with 500 mg membrane protein, and 3 nM [3H](+)-pentazocine (for S1R assays) or 5 nM [3H]DTG plus 1 mM dextrallorphan (for S2R assays); non-specific binding was determined in the presence of 10 mM haloperidol. The total reaction volume in each tube was 1.0 ml and the assays were run in triplicate, in deep well 96 well plates. Samples were filtered through glass fiber filters pre-soaked in 0.5% polyethyleneimine to minimize non-specific binding, using a Tomtech Cell Harvester, and counted in a Betaplate Reader (Wallac).

[0185] ***Data analysis.*** Saturation isotherms was conducted, and the binding sites were initially characterized for binding affinity (K_i) of the radioligands and maximal binding capacity (B_{max}). K_i values for the test compounds were calculated as previously described (Cheng and Prusoff,

1973; McLaughlin et al., 1995). Least squares fit was used to determine IC_{50} values and K_i values were calculated using equation 2.1 and 2.2.

$$Ki = \frac{IC50}{1 + S}$$

$$S = \frac{\text{concentration of radioligand}}{KD\ of\ radioligand}$$

[0186] Hill coefficients and goodness of fits for S1R versus S2R (or vice versa) sites were evaluated. Data were analyzed using GraphPad Prism 8.0 software.

[0187] ***Caco-2 Cell Culture and permeability study:***

[0188] Caco-2 cells were cultured in DMEM cell culture medium supplemented with 10% fetal bovine serum, 1% nonessential amino acids, 100 U/mL penicillin, and 100 µg/mL streptomycin and grown in a humidified atmosphere of 5% CO_2 at 37°C in T-75 flasks. The medium was changed every alternate day and after reaching 80 - 90% confluence, cells were detached from the flask by trypsinization and then seeded onto Transwell® polycarbonate inserts in 96-well plates at a density of 0.65 x 10^5 cells/cm^2. At 21 to 25 days after seeding, transepithelial electrical resistance values across the cell monolayer was measured using a Millicell-ERS volt-ohmmeter (Millipore Corporation, Billerica, MA). Inserts with trans-epithelial electrical resistance values ≥ 300 Ω.cm^2 in culture medium were used for the experiments. The cell monolayer was washed twice with warm Hanks' balanced salt solution containing 25 mM HEPES, pH 7.4 (HBSS). The test compounds in DMSO or other suitable organic solvents were diluted with HBSS to a concentration of 10µM. The apical to basolateral transport was determined by adding HBSS (75 µL) with the desired concentration of test compound to the apical chamber and 235 µL of HBSS to the basolateral side. Control compounds will also be included in the permeability experiment. To check the membrane integrity, lucifer yellow was used as zero permeability, caffeine and propranolol as high permeability, and atenolol as low permeability markers along with test compounds in each batch of study. Samples (25 µL) will be withdrawn from both chambers and precipitated using acetonitrile or methanol containing internal standard for analysis of the test and control compounds by UPLC-MS/MS after 2 h post-incubation. The apparent permeability (P_{app}) was calculated using the equation.

[0189] $P_{app} = \left(\frac{V_A}{A\ X\ t}\right) X \left(\frac{[Drug]_{Acceptor}}{[Drug]_{initial,\ donor}}\right)$

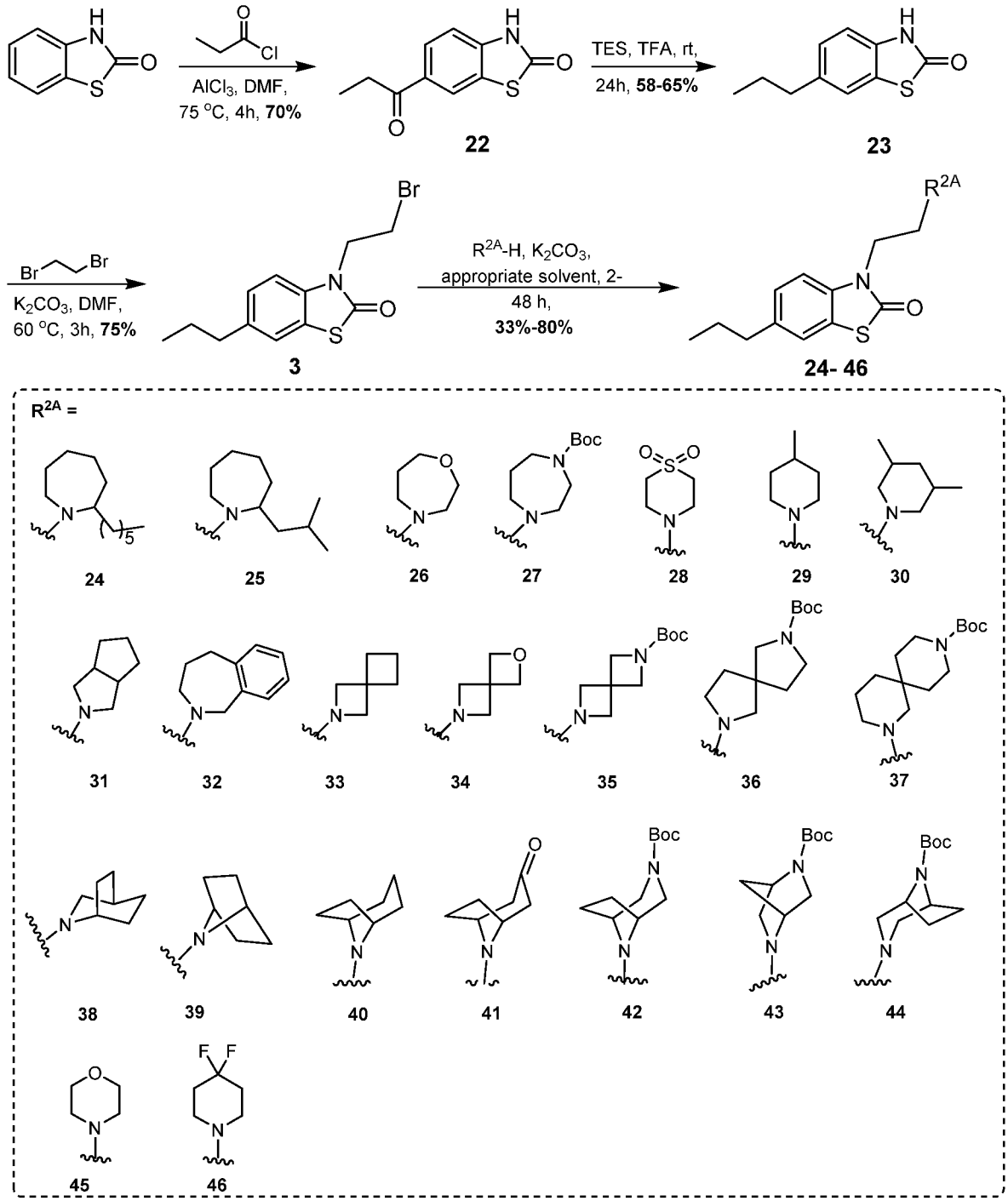
[0190] Where, 'V_D' is donor volume (0.075 mL); 'V_A' is acceptor volume (0.235 mL); 'A' is the membrane surface area (0.143 cm^2); and 't' is incubation time (in seconds). The permeability was assessed in triplicate. The compounds with apparent permeability of less than 5 x 10^{-6} cm/sec were considered as low permeability and compounds those with apparent permeability of greater than 5 x 10^{-6} cm/sec were considered as high permeability compounds.

Compounds of Formula (I)

Synthesis

[0191] The below scheme exemplifies the synthetic route utilized to prepare compounds of Formula (I).

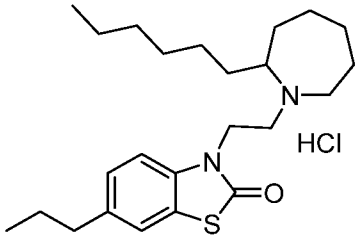
[0192] Scheme 1A: Synthesis of Compounds of Formula (I)



[0193] The synthesis of twenty-three final analogs bearing different *N*-hetercycles as a replacment of the azpane ring are summarized in Scheme 1A. The requisite intermediate **22** was synthesized via a Friedel-Crafts acylation using aluminum chloride ($AlCl_3$) in dimethylformamide (DMF). Subsequent reduction of the carbonyl group using triethylsilane in trifluoroacetic acid afforded the 6-propyl derivative **23**. The next step involved the alkylation of **23** with 1,2 dibromoethane to give intermediate **3** in 75% yield (R. Bhat, J. A. Fishback, R. R. Matsumoto, J. H. Poupaert and C. R. McCurdy, Bioorg. Med. Chem. Lett., 2013, 23, 5011-5013). Then, the alkylation with various aliphatic heterocycles gave the inspired analogs **24-46**. Finally, the hydrochloride salts were obtained for most of the analogs except **33-35**. The acid catalyzed deprotection of the tert-butoxycarbonyl (boc) protected amines with hydrochloric acid produced hydrochloride salts for compounds **27**, **36**, **37**, **42-44**. Deprotection of compound **35** was performed utilizing trifluoracetic acid (TFA), to avoid ring opening, that afforded the trifluoracetic acid salt. Also, the oxalate salts were obtained for spirocyclic compounds **33** and **34** to avoid using hydrochloric acid (HCl) and opening of the strained rings. The hydrochloride salt of **44** was hygroscopic and sticky, so it was converted to the oxalate salt to improve its handling after free basing with sodium bicarbonate ($NaHCO_3$) of the hydrochloride salt, extraction and purification with column chromatography.

[0194] General procedure C for the synthesis of 6-propyl benzothiazolones bearing different *N*-aliphatic heterocyclic amines (24-46). A solution of 3-(2-bromoethyl)-6-propylbenzo[d] thiazol-2(3H)-one **3** was added to a mixture of *N*- heterocyclic amine and inorganic base in the appropriate solvent. The reaction mixture was left to stir for 2-48 h. The time, temperature, and work up are reported for each compound separately.

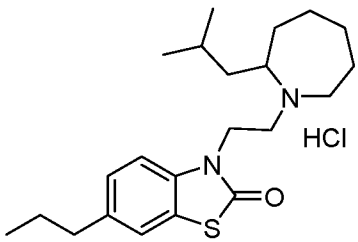
[0195] 3-(2-(2-hexylazepan-1-yl)ethyl)-6-propylbenzo[d]thiazol-2(3H)-one hydrochloride, HA121 (24)



24, HA121

[0196] A solution of 3-(2-bromoethyl)-6-propylbenzo[d] thiazol-2(3H)-one **3** (254 mg, 0.85 mmol, 1 equiv.) in THF (2 mL) was added to a mixture of 2-hexylazepane (233 mg, 1.27 mmol, 1.5 equiv.) and potassium carbonate (351 mg, 2.54 mmol, 3.0 equiv.) in 3 mL THF. The reaction mixture was refluxed for 48 h. After completion, the mixture was filtered, and the filtrate was evaporated. The crude compound was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **24** (114 mg, 33.4%). The free base (114 mg, 0.28 mmol) was dissolved in diethyl ether then excess 2M HCl/diethyl ether was added to yield the hydrochloride salt of **24**. HCl salt was triturated with diethyl ether to give a transparent oil (118 mg, combined yields 31.7%). **^{1}H NMR**: (600 MHz, Methanol-d_4) (mixture of diastereomers are overlapping), δ 7.43 (m, 2H), 7.35 (m, 2H), 7.27 (m, 2H), 4.57 – 4.35 (m, 4H), 3.65 – 3.36 (m, 10H), 2.64 (t, J = 7.6 Hz, 4H), 2.08 – 1.61 (m, 24H), 1.44 – 1.24 (m, 16H), 0.94 (t, J = 7.3 Hz, 6H), 0.90 (t, J = 6.9 Hz, 6H). **^{13}C NMR** (JMOD, 151 MHz, MeOD): δ 172.60 (2C), 140.28 (2C), 135.45 (2C), 128.49 (2C), 123.89 (2C), 123.62 (2C), 111.89 (2C), 69.30, 66.86, 54.52, 53.66, 53.16, 39.19, 38.88, 38.51, 33.12, 32.66 (2C), 30.18, 30.12, 29.97, 29.01, 28.56 (2C), 27.40, 27.22, 27.00, 25.86, 24.71, 24.54, 24.30 (2C), 23.58, 14.36, 13.92. **NB**: Spectrum represents a mixture of two diastereomers (eighteen additional carbon signals correspond to six additional aromatic carbons, one additional carbonyl, and eleven additional aliphatic carbons; i.e. only six carbon signals are missing due to overlap from the two isomers). **UPLC/MS (Method A)**: t_R = 3.05 min, MS (ESI+) m/z = 403.56 $[M+H]^+$. **HRMS (ESI) for $C_{24}H_{39}N_2OS^+$**: Theoretical $[M+H]^+$= 403.2778 (4.2 ppm); found 403.2761.

[0197] 3-(2-(2-isobutylazepan-1-yl)ethyl)-6-propylbenzo[d]thiazol-2(3H)-one hydrochloride, HA126 (25)

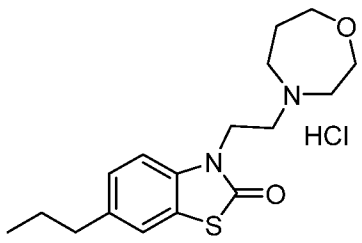


25, HA126

[0198] A solution of 3-(2-bromoethyl)-6-propylbenzo[d] thiazol-2(3H)-one **3** (200 mg, 0.67 mmol, 1 equiv.) in THF (1 mL) was added to a mixture of 2-isobutylazepane (155 mg, 0.99 mmol, 1.5 equiv.) and potassium carbonate (276 mg, 1.99 mmol, 3.0 equiv.) in THF (3 mL). The

reaction mixture was refluxed for 48 h. After being cooled, the mixture was filtered, and the filtrate was evaporated. The crude compound was purified by silica gel chromatography using a gradient of hexanes and ethyl acetate to afford **25** (111 mg, 44.4%). HCl salt was prepared by dissolving the free base (93 mg, 0.25 mmol) in diethyl ether then excess 2M HCl/diethyl ether was added to yield the hydrochloride salt of **25** as a white solid (100 mg, 98% yield). **^{1}H NMR** (600 MHz, Methanol-d_4) (mixture of diastereomers are overlapping), δ 7.42 (dd, J = 4.8, 1.7 Hz, 2H), 7.39 – 7.34 (m, 2H), 7.28 – 7.25 (m, 2H), 4.53 – 4.39 (m, 4H), 3.73 – 3.42 (m, 10H), 2.64 (t, J = 7.5 Hz, 4H), 2.10 – 1.75 (m, 13H), 1.75 – 1.61 (m, 11H), 1.56 – 1.45 (m, 2H), 1.01 (d, J = 6.4 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.4 Hz, 3H), 0.94 (t, J = 7.4 Hz, 6H), 0.90 (d, J = 6.6 Hz, 3H). **^{13}CNMR** (JMOD, 151 MHz, MeOD): δ 172.69 (2C), 140.32 (2C), 135.51 (2C), 128.49 (2C), 123.92 (2C),123.63 (2C), 111.94 (2C), 67.71, 65.09, 54.40, 53.44, 52.89, 49.48, 41.80, 39.17, 38.83, 38.49, 38.22, 29.24, 28.84, 28.67, 26.85, 26.64, 26.27, 25.86, 24.86, 24.58, 24.34, 24.18, 24.07, 23.83, 21.40, 21.16, 13.90. **NB**: Spectrum represents a mixture of two diastereomers (nineteen additional carbon signals correspond to six additional aromatic carbons, one additional carbonyl, and twelve additional aliphatic carbons; i.e. only three carbon signals are missing due to overlap from the two isomers). **UPLC/MS (Method A)**: t_R = 3.29 min, MS (ESI+) m/z = 375.51 $[M+H]^+$. **HRMS (ESI) for $C_{22}H_{35}N_2OS^+$**: Theoretical $[M+H]^+$= 375.3465 (3.2 ppm); found 375.2453.

[0199] 3-(2-(1,4-oxazepan-4-yl)ethyl)-6-propylbenzo[d]thiazol-2(3H)-one hydrochloride, HA70 (26)

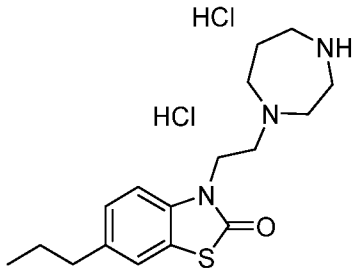


26, HA70

[0200] A solution of 3-(2-bromoethyl)-6-propylbenzo[d] thiazol-2(3H)-one **3** (356 mg, 1.18 mmol, 1.2 equiv.) in DMF (2 mL), was added to a solution of 1,4-oxazepane (100 mg, 0.98 mmol, 1 equiv.) in DMF (2 mL), and potassium carbonate (410 mg, 2.96 mmol, 3.0 equiv.). The reaction mixture was stirred at room temperature overnight. Then, the reaction mixture was poured onto water, and the aqueous layer was extracted with DCM. The combined organic layers

were washed with brine, dried with Na_2SO_4, filtered, and the solvent was evaporated *in vacuo*. The crude compound was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **26** (138.5 mg, 36.5%). HCl salt was prepared by dissolving the free base(138.5 mg, 0.43 mmol) in diethyl ether, then excess 2M HCl/diethyl ether was added to yield the hydrochloride salt as a white solid (148 mg, combined yield 41.9%). **^{1}H NMR** (600 MHz, Methanol-d4) δ 7.41 (dd, J = 4.8, 1.6 Hz, 1H), 7.34 (dd, J = 11.0, 7.1 Hz, 1H), 7.25 (dd, J = 8.3, 1.8 Hz, 1H), 4.45 (td, J = 6.6, 2.9 Hz, 2H), 3.99 – 3.71 (m, 6H), 3.61 (t, J = 6.5 Hz, 2H), 3.56 – 3.39 (m, 2H), 2.63 (t, J = 7.5 Hz, 2H), 2.33 – 2.12 (m, 2H), 1.68 – 1.61 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (151 MHz, MeOD) δ 172.67, 140.21, 135.47, 128.43, 123.81, 123.68, 111.92, 68.90, 64.58, 58.21, 55.23, 54.95, 38.74, 38.51, 27.23, 25.87, 13.92. **UPLC/MS (Method A)**: t_R = 2.93 min, MS (ESI+) *m/z* = 321.28 $[M+H]^+$. **HRMS (ESI) for $C_{17}H_2N_2O_2S^+$**: Theoretical $[M+H]^+$= 321.1631(2.8 ppm); found 321.1622.

[0201] 3-(2-(1,4-diazepan-1-yl)ethyl)-6-propylbenzo[d]thiazol-2(3H)-one hydrochloride, HA188 (27)

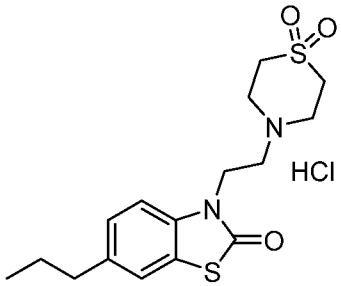


27, HA188

[0202] A solution of 3-(2-bromoethyl)-6-propylbenzo[d] thiazol-2(3H)-one **3** (200 mg, 0.67 mmol, 1 equiv.) in THF (2 mL) was added to a mixture of tert-butyl 1,4-diazepane-1-carboxylate (200 mg, 0.99 mmol, 1.5 equiv.) and potassium carbonate (276 mg, 1.99 mmol, 3.0 equiv.) in 3 mL THF. The reaction mixture was refluxed for 30 h. After being cooled, the mixture was filtered, and the filtrate was evaporated. The crude compound was purified by silica gel chromatography using a gradient of hexanes and ethyl acetate to afford **22** (222 mg, 79% yield). Boc group deprotection: To a solution of **27** (120 mg, mmol) in methanol, excess 4N HCl in dioxane (1.5 mL) was added. The reaction mixture was stirred at room temperature for 48 h, then crystalized from ethanol to afford the final compound as a white solid of the dihydrochloride salt in good yield (83 mg, 74%). **^{1}H NMR** ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.42 (d, J = 1.8 Hz,

1H), 7.35 (d, J = 8.3 Hz, 1H), 7.26 (dd, J = 8.3, 1.7 Hz, 1H), 4.48 (t, J = 6.5 Hz, 2H), 3.99 – 3.82 (m, 2H), 3.74 (t, J = 4.6 Hz, 2H), 3.64 (t, J = 6.2 Hz, 4H), 3.49 (t, J = 5.8 Hz, 2H), 2.64 (t, J = 7.6 Hz, 2H), 2.35 (p, J = 5.3 Hz, 2H), 1.65 (hex, J = 7.4 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (JMOD, 151 MHz, MeOD) δ 172.90, 140.28, 135.45, 128.45, 123.83, 123.73, 111.98, 55.65, 55.58, 51.47, 45.79, 42.30, 38.79, 38.51, 25.87, 22.44, 13.91. **UPLC/MS (Method A)**: t_R = 2.16 min, MS (ESI+) m/z = 320.34 $[M+H]^+$. **HRMS (ESI) for $C_{17}H_{26}N_3OS^+$**: Theoretical $[M+H]^+$= 320.1791 (1.2 ppm); found 320.1787.

[0203] 3-(2-(1,1-dioxidothiomorpholino)ethyl)-6-propylbenzo[d]thiazol-2(3H)-one hydrochloride, HA143 (28)

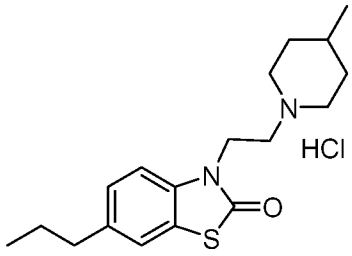


28, HA143

[0204] A solution of 3-(2-bromoethyl)-6-propylbenzo[d] thiazol-2(3H)-one **3** (200 mg, 0.67 mmol, 1 equiv.) in THF (3 mL) was added to a mixture of thiomorpholine 1,1-dioxide (135 mg, 0.99 mmol, 1.5 equiv.) and potassium carbonate (276 mg, 1.99 mmol, 3.0 equiv.) in THF (3 mL). Then, tetrabutylammonium iodide (123 mg, 0.33 mmol, 0.5 equiv.) was added after 3 h as no product was observed by LCMS. The reaction mixture was refluxed for additional 27 h. After being cooled, the mixture was filtered, and the filtrate was evaporated. The crude compound was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **28** (90 mg, 39.1%). HCl salt was prepared by dissolving the free base (41 mg, 0.12 mmol) in DCM, then excess 2M HCl/diethyl ether was added to yield the hydrochloride salt as a white solid (42.5 mg, 94%). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.51 (d, J = 1.7 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.22 (dd, J = 8.3, 1.8 Hz, 1H), 4.34 (t, J = 7.1 Hz, 2H), 3.84 – 3.37 (m, 10H), 2.58 (t, J = 7.5 Hz, 2H), 1.59 (hex, J = 7.4 Hz, 2H), 0.89 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (JMOD, 151 MHz, DMSO) δ 178.58, 147.21, 143.69, 136.33, 132.01, 130.96, 120.80, 60.70, 59.66, 57.57, 46.89, 46.23, 33.75, 23.01. **N.B**: two carbons are overlapping. **UPLC/MS (Method B)**: t_R = 3.78 min, MS (ESI+) m/z

=355.39 $[M+H]^+$. **HRMS (ESI) for $C_{16}H_{23}N_2O_3S_2^+$**: Theoretical $[M+H]^+$= 355.1145 (2.3 ppm), $[M+Na]^+$= 377.0964 (3.2 ppm); found 355.1137 and 377.095, respectively.

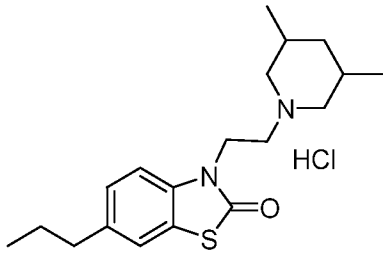
[0205] 3-(2-(4-methylpiperidin-1-yl)ethyl)-6-propylbenzo[d]thiazol-2(3H)-one hydrochloride, HA71 (29)



29, HA71

[0206] A solution of 3-(2-bromoethyl)-6-propylbenzo[d] thiazol-2(3H)-one **3** (250 mg, 0.83 mmol, 1.2 equiv.) in DMF (2 mL) was added under argon to a solution of 4-methylpiperidine (84 µL, 0.69 mmol, 1 equiv.), and potassium carbonate (287.7 mg, 2.08 mmol, 3.0 equiv.) in DMF (2 mL). The reaction mixture was stirred at room temperature overnight. Then, the reaction mixture was poured onto water, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with brine, dried with Na_2SO_4, filtered, and the solvent was evaporated *in vacuo*. The crude compound was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **29** (148 mg, 67%). HCl salt was prepared by dissolving the free base (148 mg, 0.46 mmol) in diethyl ether, then excess 2M HCl/diethyl ether was added and the mixture was left to stir overnight to yield the hydrochloride salt. Crystallization from isopropanol was carried out to give **29** as a white solid (66 mg, combined yield 26.8%). **^{1}H NMR** (600 MHz, Methanol-d4) δ 7.40 (d, J = 1.6 Hz, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.25 (dd, J = 8.3, 1.6 Hz, 1H), 4.44 (t, J = 6.6 Hz, 2H), 3.76 (d, J = 11.8 Hz, 2H), 3.48 (t, J = 6.5 Hz, 2H), 3.07 (t, J = 12.8 Hz, 2H), 2.63 (t, J = 7.6 Hz, 2H), 1.98 – 1.92 (m, 2H), 1.80 – 1.69 (m, 1H), 1.65 (hex, J = 7.4 Hz, 2H), 1.52 (t, J = 13.9 Hz, 2H), 1.02 (d, J = 6.5 Hz, 3H), 0.94 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (151 MHz, MeOD) δ 172.65, 140.15, 135.48, 128.40, 123.77, 123.69, 111.92, 55.11, 54.60, 38.50, 38.34, 32.46, 29.79, 25.87, 21.39, 13.92. **N.B**: two carbons are overlapping. **UPLC/MS (Method A)**: t_R = 3.38 min, MS (ESI+) *m/z* = 319.30 $[M+H]^+$. **HRMS (ESI) for $C_{18}H_{27}N_2OS^+$**: Theoretical $[M+H]^+$= 319.1855 (5.0 ppm); found 319.1855.

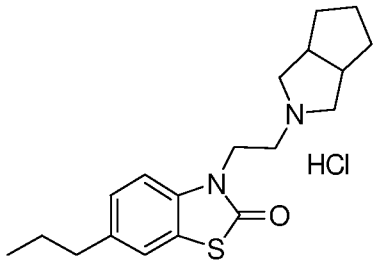
[0207] 3-(2-(3,5-dimethylpiperidin-1-yl)ethyl)-6-propylbenzo[d]thiazol-2(3H)-one hydrochloride, MH-S3 (30)



30, MH-S3

[0208] A solution of 3-(2-bromoethyl)-6-propylbenzo[d]thiazol-2(3H)-one **3** (460 mg, 1.53 mmol, 1 equiv.) in DMF (1 mL) was added slowly to a mixture of cis/trans-3,5-dimethylpiperidine (0.24 mL, 1.83 mmol, 1.2 equiv.), cesium carbonate (1720 mg, 5.29 mmol, 3.5 equiv.), and catalytic amount of potassium iodide in DMF (4 mL) under argon. Then, the reaction mixture was heated at 60 °C for 24 h. The mixture was poured onto water then was extracted with ethyl acetate. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and the solvent was evaporated *in vacuo*. The crude compound was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **30** (213 mg, 41.8%). HCl salt was prepared by dissolving the free base (100 mg, 0.30 mmol) in diethyl ether, then excess 2M HCl/diethyl ether was added and the mixture was left to stir overnight to yield the hydrochloride salt, which was triturated with diethyl ether and filtered to yield **30** as while solid (105 mg, 94.6%). **^{1}H NMR** (600 MHz, Methanol-d4) (mixture of diastereomers are overlapping), δ 7.44 – 7.39 (m, 2H), 7.37 – 7.30 (m, 2H), 7.26 (dd, *J* = 8.3, 1.9 Hz, 2H), 4.52 – 4.39 (m, 4H), 3.67 (dd, *J* = 11.4, 4.5 Hz, 4H), 3.49 (t, *J* = 6.4 Hz, 4H), 2.70 – 2.54 (m, 8H), 2.05 – 1.92 (m, 4H), 1.92 – 1.83 (m, 2H), 1.70 – 1.60 (m, 4H), 1.02 (dd, *J* = 6.6, 1.6 Hz, 13H), 0.96 – 0.87 (m, 7H). **^{13}C NMR** (151 MHz, MeOD) δ 172.75 (2C), 140.21 (2C), 135.49, 128.45 (2C), 123.82 (2C), 123.72 (2C), 112.02 (2C), 59.61, 55.35 (2C), 40.13 (2C), 38.51 (2C), 38.33 (2C), 30.60 (2C), 25.88, 18.71 (2C), 13.92 (2C). **N.B**: Spectrum represents a mixture of two diastereomers; i.e. only nine carbon signals are missing due to overlap from the two isomers). **UPLC/MS (Method A)**: t_R = 3.26 min, MS (ESI+) *m/z* = 333.25 $[M+H]^+$. **HRMS (ESI) for $C_{19}H_{29}N_2OS^+$**: Theoretical $[M+H]^+$= 333.1993 (0.1 ppm); found 333.1994.

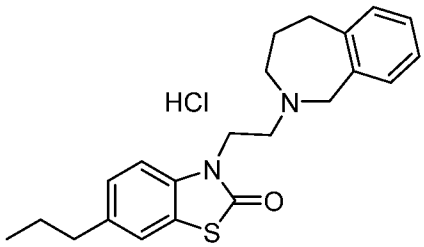
[0209] 3-(2-(hexahydrocyclopenta[c]pyrrol-2(1H)-yl)ethyl)-6-propylbenzo[d]thiazol-2(3H)-one hydrochloride, HA201/ MH-S4 (31)



31, HA201/ MH-S4

[0210] A solution of 3-(2-bromoethyl)-6-propylbenzo[d] thiazol-2(3H)-one **3** (200 mg, 0.66 mmol, 1 equiv.) in ***N*-Methyl-2-pyrrolidone,** NMP, (2 mL) was added to o a solution of octahydrocyclopenta[c]pyrrole (111 mg, 0.99 mmol, 1.5 equiv.), and potassium carbonate (276 mg, 1.99 mmol, 3.0 equiv.) in NMP (2 mL). The reaction mixture was stirred at 60 °C overnight. After cooling, the reaction mixture was poured onto water, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and the solvent was evaporated *in vacuo*. The crude compound was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **31** (88 mg, 40%). HCl salt was prepared by dissolving the free base (88 mg, 26.6 mmol) in diethyl ether, then excess 2M HCl/diethyl ether was added and the mixture was left to stir overnight to yield the hydrochloride salt. After evaporation, the residue was triturated with diethyl ether and filtered to give the HCl salt of **31** as buff solid (93 mg, combined yield 38.4%). **^{1}H NMR** (600 MHz, Methanol-d_4) δ 7.44 (d, J = 1.3 Hz, 1H), 7.32 – 7.25 (m, 2H), 4.40 (t, J = 5.9 Hz, 2H), 4.06 – 4.01 (m, 2H), 3.66 – 3.55 (m, 2H), 3.04 – 2.69 (m, 4H), 2.66 (t, J = 7.7 Hz, 2H), 1.86 – 1.45 (m, 8H), 0.96 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (JMOD,151 MHz, MeOD) δ 171.68, 138.99, 127.14, 122.58, 122.49, 110.57, 59.66, 51.12, 48.15, 41.24, 38.62, 37.23, 30.29, 24.60, 23.83, 12.62. **NB**: Three carbons are overlapping. **UPLC/MS (Method A)**: t_R = 2.59 min, MS (ESI+) 331.27 $(M+H)^+$. **HRMS (ESI) for $C_{19}H_{27}N_2OS^+$**: Theoretical $[M+H]^+$= 331.1839 (3.0ppm); found 331.1849.

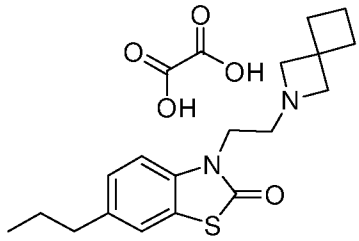
[0211] 6-propyl-3-(2-(1,3,4,5-tetrahydro-2H-benzo[c]azepin-2-yl)ethyl)benzo[d]thiazol-2(3H)-one hydrochloride, MH-S7 (32)



32, MH-S7

[0212] A solution of 3-(2-bromoethyl)-6-propylbenzo[d] thiazol-2(3H)-one **3** (244 mg, 0.81 mmol, 1.2 equiv.) in DMF (2 mL) was added to a solution of 2,3,4,5-tetrahydro-1H-benzo[c]azepine (100 mg, 0.68 mmol, 1 equiv.), cesium carbonate (660 mg, 2.03 mmol, 3.0 equiv.), and traces of potassium iodide in DMF (3 mL) under argon. The reaction mixture was stirred at 60 °C for 3 h, then left to stir at room temperature overnight. Then, the reaction mixture was poured onto water, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with brine, dried with Na_2SO_4, filtered, and the solvent was evaporated *in vacuo*. The crude compound was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **32** (82 mg, 33%). HCl salt was prepared by dissolving the free base (82 mg, 0.22 mmol) in diethyl ether, then excess 2M HCl/diethyl ether was added and the mixture was left to stir overnight. After evaporation, the residue was triturated with diethyl ether and filtered to yield the hydrochloride salt as white solid (88 mg, combined yield 32.1%). **^{1}H NMR** (600 MHz, Methanol-d4) δ 7.51 – 7.48 (m, 1H), 7.41 – 7.36 (m, 2H), 7.30 (dd, J = 8.4, 6.8 Hz, 2H), 7.26 – 7.22 (m, 2H), 4.69 (s, 2H), 4.45 (t, J = 6.8 Hz, 2H), 3.78 – 3.69 (m, 2H), 3.51 – 3.40 (m, 2H), 3.09 (t, J = 5.8 Hz, 2H), 2.63 (t, J = 7.6 Hz, 2H), 2.11 – 2.02 (m, 2H), 1.65 (hex, J = 7.4 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (151 MHz, MeOD) δ 172.62, 144.51, 140.21, 135.46, 133.10, 131.53, 130.68, 130.46, 128.38, 123.82, 123.67, 111.85, 60.04, 59.27, 38.61, 38.51, 34.37, 25.88, 13.92. **NB**: Three carbons are overlapping. **UPLC/MS (Method A)**: t_R = 3.05 min, MS (ESI+) *m/z* = 367.28 $[M+H]^+$. **HRMS (ESI) for $C_{22}H_{27}N_2OS^+$**: Theoretical $[M+H]^+$= 367.1839 (0.8 ppm); found 367.1836.

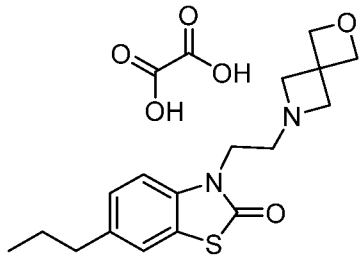
[0213] 3-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-6-propylbenzo[d]thiazol-2(3H)-one oxalate, HA111 (33)



33, HA111

[0214] A solution of 3-(2-bromoethyl)-6-propylbenzo[d] thiazol-2(3H)-one **3** (200 mg, 0.67 mmol, 1.2 equiv.) was added to a mixture of 2-azaspiro[3.3]heptane hemioxalate (157.8 mg, 0.56 mmol, 1 equiv.) and potassium carbonate (230.2 mg, 1.66 mmol, 3.0 equiv.) in acetonitrile, ACN, (10 mL). The reaction mixture was heated at 60 °C for 3.5 h. After being cooled, the volatile solvent was evaporated, and the compound were extracted with ethyl acetate. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and the solvent was evaporated *in vacuo*. The crude compound was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **33** (125 mg, 71%). This reaction was repeated with the same conditions except that I added 0.5 mL of DMF as a co-solvent and the reaction was heated for 5 h to afford **33** in lower yield (70 mg, 39.8%). Oxalate salt was prepared by dissolving the free base (70 mg, 0.22 mmol, 1 equiv.) in diethyl ether, then a solution of oxalic acid (30 mg, 0.33 mmol, 1.5 equiv.) in diethyl ether was added and the mixture was stirred overnight. The salt was triturated with diethyl ether, then filtered to yield the oxalate salt as a white solid (72.4 mg, combined yield 26.7%). **^{1}H NMR** (600 MHz, Methanol-d4) δ 7.37 (d, J = 1.5 Hz, 1H), 7.28 (d, J = 8.3 Hz, 1H), 7.21 (dd, J = 8.3, 1.7 Hz, 1H), 4.31 – 4.28 (m, 2H), 4.25 (t, J = 5.7 Hz, 2H), 4.18 – 4.14 (m, 2H), 3.59 (t, J = 5.8 Hz, 2H), 2.62 – 2.58 (m, 2H), 2.35 (t, J = 7.7 Hz, 2H), 2.24 (t, J = 7.8 Hz, 2H), 1.85 (p, J = 7.7 Hz, 2H), 1.62 (hex, J = 7.4 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (JMOD,151 MHz, MeOD) δ 172.54, 166.45, 140.10, 135.46, 128.36, 123.73, 123.56, 111.83, 66.98, 53.53, 39.37, 39.00, 38.52, 33.03, 25.84, 16.65, 13.94. **NB**: Two carbons are overlapping. **UPLC/MS (Method A)**: t_R = 4.08 min, MS (ESI+) *m/z* = 317.37 $[M+H]^+$. **HRMS (ESI) for $C_{18}H_{25}N_2OS^+$**: Theoretical $[M+H]^+$= 317.1682 (0.6 ppm); found 317.1680.

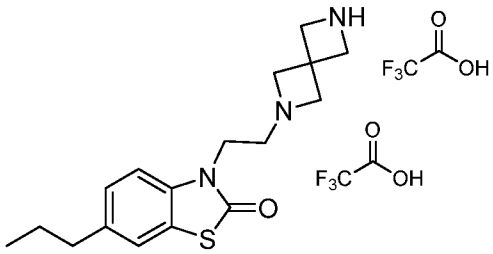
[0215] 3-(2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)ethyl)-6-propylbenzo[d]thiazol-2(3H)-one oxalate, HA109 (34)



34, HA109

[0216] A solution of 3-(2-bromoethyl)-6-propylbenzo[d] thiazol-2(3H)-one **3** (150 mg, 0.49 mmol, 1.2 equiv.) in ACN (6 mL) was added to a mixture of 2-oxa-6-azaspiro[3.3]heptane (41.3 mg, 0.42 mmol, 1 equiv.) and potassium carbonate (172.6 mg, 1.25 mmol, 3.0 equiv.) in ACN (10 mL). The reaction mixture was heated at 60 °C for 3 h. After being cooled, the mixture was filtered, and the filtrate was evaporated *in vacuo*. The crude compound was purified by silica gel chromatography using a gradient of ethyl acetate and methanol to afford **34** (91 mg, 68.6%). Oxalate salt was prepared by dissolving **34** (65 mg, 0.20 mmol, 1 equiv.) in diethyl ether, then a solution of oxalic acid (18 mg, 0.20 mmol, 1 equiv.) in diethyl ether was added and the mixture was stirred for 2 h. The solid was triturated with diethyl ether, then filtered to yield the oxalate salt as a white solid (82 mg, combined yield 48.2%). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.50 (d, J = 1.6 Hz, 1H), 7.28 (d, J = 8.3 Hz, 1H), 7.20 (dd, J = 8.3, 1.7 Hz, 1H), 4.61 (s, 4H), 4.05 (t, J = 5.9 Hz, 2H), 3.98 (s, 4H), 3.22 (t, J = 5.9 Hz, 2H), 2.57 (t, J = 7.5 Hz, 2H), 1.58 (hex, J = 7.3 Hz, 2H), 0.88 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (JMOD, 151 MHz, DMSO) δ 169.20, 163.46, 137.58, 134.43, 126.78, 122.45, 121.42, 111.19, 79.00, 62.42, 52.18, 38.52, 37.95, 36.74, 24.28, 13.52. **NB**: Two carbons are overlapping. **UPLC/MS (Method A)**: t_R = 3.16 min, MS (ESI+) m/z = 319.37 $[M+H]^+$. **HRMS (ESI) for $C_{17}H_{23}N_2O_2S^+$**: Theoretical $[M+H]^+$= 319.1475 (3.4 ppm); found 319.1464.

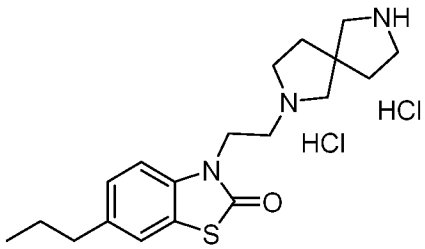
[0217] 3-(2-(2,6-diazaspiro[3.3]heptan-2-yl)ethyl)-6-propylbenzo[d]thiazol-2(3H)-one bis(2,2,2-trifluoroacetate), HA135 (35)



35, HA135

[0218] A solution of 3-(2-bromoethyl)-6-propylbenzo[d] thiazol-2(3H)-one **3** (150 mg, 0.49 mmol, 1 equiv.) in THF (2 mL) was added to a mixture of tert-butyl 2,6-diazaspiro[3.3] heptane-2-carboxylate hemioxalate (182.3 mg, 0.37 mmol, 0.75 equiv.), and potassium carbonate (414.27 mg, 2.99 mmol, 6.0 equiv.) in THF (4 mL). The reaction mixture was heated at 60 °C for 48 h and checked by LCMS for completion. Then, the reaction mixture was poured onto water, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with brine, dried with Na_2SO_4, filtered, and the solvent was evaporated *in vacuo*. The crude compound was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **30** (169 mg, 81%). Boc group deprotection: To a solution of **35** (25 mg, 0.059 mmol) in DCM (2 mL), (2 mL) TFA was added. The reaction mixture was stirred overnight at room temperature. The solvents were removed by evaporation and the residue was triturated with diethyl ether to yield **35** (31.4 mg, 96.3%) as a buff solid of the ditrifluoroacetate salt. **^{1}H NMR salt** (600 MHz, Methanol-d_4) δ 7.42 (d, J = 1.6 Hz, 1H), 7.24 (dd, J = 8.3, 1.7 Hz, 1H), 7.20 (d, J = 8.3 Hz, 1H), 4.36 (s, 4H), 4.28 (s, 4H), 4.25 (t, J = 5.5 Hz, 2H), 3.57 – 3.52 (m, 2H), 2.63 (t, J = 7.8 Hz, 2H), 1.65 (hex, J = 7.4 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (JMOD, 151 MHz, MeOD) δ 172.59, 163.07 (q, J = 35.2 Hz), 140.20, 135.38, 128.37, 123.76, 123.65, 118.10 (q, J = 293.5 Hz), 111.78, 63.91, 60.84, 53.44, 38.99, 38.51, 37.15, 25.82,13.89. **NB**: Two carbons are overlapping. **UPLC/MS (Method B)**: t_R = 2.28 min, MS (ESI+) m/z = 318.36 $[M+H]^+$. **HRMS (ESI) for $C_{17}H_{24}N_3OS^+$**: Theoretical $[M+H]^+$= 318.1635 (5.0 ppm); found 318.1651.

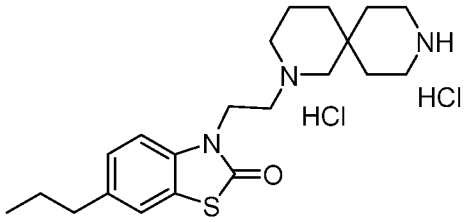
[0219] 3-(2-(2,7-diazaspiro[4.4]nonan-2-yl)ethyl)-6-propylbenzo[d]thiazol-2(3H)-one dihydrochloride, HA99 (36)



36, HA99

[0220] 3-(2-bromoethyl)-6-propylbenzo[d] thiazol-2(3H)-one **3** (150 mg, 0.49 mmol, 1.2 equiv.) was added as a solid to a mixture of tert-butyl 2,7-diazaspiro[4.4]nonane-2-carboxylate (94.2 mg, 0.42 mmol, 1 equiv.) and potassium carbonate (172.6 mg, 1.25 mmol, 3.0 equiv.) in ACN (10 mL). The reaction mixture was heated at 60 °C for 3 h. After being cooled, the mixture was filtered, and the filtrate was evaporated. The crude compound was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **36** (106.5 mg, 57.4%). Boc group deprotection: To a solution of **36** (106.5 mg, mmol) in DCM (2 mL), excess 4N HCl in dioxane (2 mL) was added. The reaction mixture was stirred overnight at room temperature. The solvents were removed by evaporation and the residue was triturated with diethyl ether to yield (96 mg, combined yield 55%) of the dihydrochloride salt as a white solid. **^{1}H NMR** (600 MHz, Methanol-d_4) (mixture of diastereomers are overlapping), δ 7.41 (d, J = 1.6 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 7.25 (dd, J = 8.3, 1.6 Hz, 2H), 4.49 – 4.38 (m, 4H), 4.07 – 3.88 (m, 4H), 3.67 (t, J = 6.1 Hz, 4H), 3.51 – 3.37 (m, 12H), 2.63 (t, J = 7.6 Hz, 4H), 2.41 – 2.11 (m, 8H), 1.65 (hex, J = 7.4 Hz, 4H), 0.94 (t, J = 7.3 Hz, 6H). **^{13}C NMR** (JMOD,151 MHz, MeOD): δ 172.75, 140.20, 135.45, 128.41, 123.78, 123.69, 112.00, 62.43 (2C), 55.27, 54.09, 53.79 (2C), 49.23, 46.09 (2C), 39.76, 38.51, 36.87, 36.52, 35.36 (2C), 25.86, 13.92. **NB**: Spectrum represents a mixture of two diastereomers (five additional carbon signals correspond to five aliphatic carbons; i.e. only fourteen carbon signals are missing due to overlap from the two isomers). **UPLC/MS (Method A)**: t_R = 2.54 min, MS (ESI$^+$) m/z = 346.43 [M+H]$^+$. **HRMS (ESI) for $C_{19}H_{28}N_3OS^+$**: Theoretical [M+H]$^+$= 346.1948 (0.6 ppm); found 346.1950.

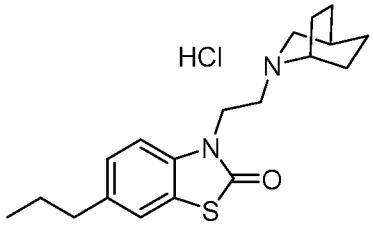
[0221] 3-(2-(2,9-diazaspiro[5.5]undecan-2-yl)ethyl)-6-propylbenzo[d]thiazol-2(3H)-one dihydrochloride, MH-S6 (37)



37, MH-S6

[0222] 3-(2-bromoethyl)-6-propylbenzo[d] thiazol-2(3H)-one **3** (293 mg, 0.98 mmol, 1.2 equiv.) was added as a solid to a mixture of tert-butyl 2,9-diazaspiro[5.5]undecane-9-carboxylate (207 mg, 0.81 mmol, 1 equiv.), potassium carbonate (795 mg, 5.75 mmol, 7 equiv.), and catalytic amount of potassium iodide in anhydrous DMF (5 mL). The reaction mixture was heated at 60 °C for 3 h under argon. Then, the reaction mixture was poured onto water, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with brine, dried with Na_2SO_4, filtered, and the solvent was evaporated *in vacuo*. The crude compound was purified by silica gel chromatography using a gradient of DCM and methanol to give **37** (193 mg, 50.3%). Boc group deprotection: To a solution of **37** (193 mg, 0.41 mmol) in DCM (2 mL), excess 4N HCl in dioxane (2 mL) was added. The reaction mixture was stirred overnight at room temperature. The solvents were removed by evaporation and the residue was triturated with diethyl ether to yield (175 mg, combined yield 48.3%) as a white solid of the dihydrochloride salt. **^{1}H NMR** (600 MHz, Methanol-d4) δ 7.41 (d, J = 1.6 Hz, 1H), 7.38 (d, J = 8.3 Hz, 1H), 7.25 (dd, J = 8.3, 1.7 Hz, 1H), 4.67 – 4.59 (m, 1H), 4.43 (dt, J = 15.4, 5.3 Hz, 1H), 4.01 (d, J = 12.6 Hz, 1H), 3.64 – 3.54 (m, 2H), 3.50 (dt, J = 12.5, 5.4 Hz, 1H), 3.42 (ddd, J = 11.4, 7.1, 3.4 Hz, 1H), 3.29 – 3.21 (m, 3H), 3.07 – 3.00 (m, 1H), 2.94 (d, J = 12.6 Hz, 1H), 2.63 (t, J = 7.6 Hz, 2H), 2.21 – 2.12 (m, 1H), 2.05 – 1.94 (m, 3H), 1.92 – 1.85 (m, 1H), 1.81 – 1.70 (m, 2H), 1.65 (hex, J = 7.4 Hz, 2H), 1.49 (td, J = 14.3, 4.0 Hz, 1H), 0.93 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (151 MHz, MeOD) δ 173.02, 140.25, 135.54, 128.45, 123.71, 112.12, 59.40, 56.74, 55.57, 40.70, 40.39, 38.51, 38.27, 34.47, 32.35, 32.04, 28.67, 25.87, 19.83, 13.91. **NB**: one carbon is overlapping. **UPLC/MS (Method A)**: t_R = 0.59 min, MS (ESI$^+$) 374.34 $(M+H)^+$. **HRMS (ESI) for $C_{21}H_{32}N_3OS^+$**: Theoretical $[M+H]^+$ = 374.2161 (3.0 ppm); found 374.2271.

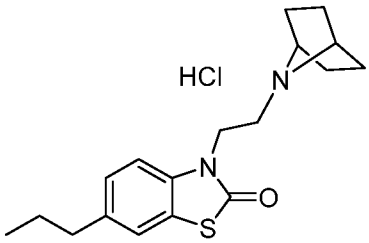
[0223] 3-(2-((1s,4s)-2-azabicyclo[2.2.2]octan-2-yl)ethyl)-6-propylbenzo[d]thiazol-2(3H)-one hydrochloride, HA170 (38)



38, HA170

[0224] A solution of 3-(2-bromoethyl)-6-propylbenzo[d] thiazol-2(3H)-one **3** (200 mg, 0.67 mmol, 1 equiv.) in THF (2 mL) was added to a mixture of (1s,4s)-2-azabicyclo[2.2.2]octane (111.1 mg, 0.99 mmol, 1.5 equiv.), and potassium carbonate (276 mg, 1.99 mmol, 3.0 equiv.) in THF (3 mL). The reaction mixture was refluxed for 20 h. After being cooled, the mixture was filtered, and the filtrate was evaporated. The residue was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **38** (187 mg, 85%). HCl salt was prepared by dissolving the free base in DCM, then excess 2M HCl/diethyl ether was added. The reaction mixture was stirred for 24h to yield the hydrochloride salt as a white solid (167 mg, combined yield 68.3%). **^{1}H NMR** (600 MHz, Methanol-d_4) δ 7.44 (d, J = 1.6 Hz, 1H), 7.35 (d, J = 8.2 Hz, 1H), 7.28 (dd, J = 8.3, 1.7 Hz, 1H), 4.43 (t, J = 6.5 Hz, 2H), 3.68 (p, J = 2.8 Hz, 1H), 3.58 (t, J = 6.5 Hz, 2H), 3.16 (br s, 1H), 2.66 (t, J = 7.6 Hz, 2H), 2.26 – 2.14 (m, 2H), 2.02 (hept, J = 2.9 Hz, 1H), 1.94 – 1.71 (m, 8H), 1.67 (hex, J = 7.4 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (JMOD,151 MHz, MeOD) δ 172.70, 140.20, 135.58, 128.42, 123.81, 123.73, 111.86, 56.83, 53.94, 52.59, 38.71, 38.51, 25.87, 24.92, 23.32(confirmed by HSQC), 22.80(confirmed by HSQC), 13.91. **NB**: Two carbons are overlapping. **UPLC/MS (Method B)**: t_R = 2.98 min, MS (ESI$^+$) 331.37 (M+H)$^+$. **HRMS (ESI) for $C_{19}H_{27}N_2OS^+$**: Theoretical [M+H]$^+$ = 331.1839 (1.8 ppm); found 331.1833.

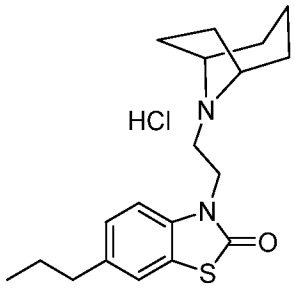
[0225] 3-(2-(7-azabicyclo[2.2.1]heptan-7-yl)ethyl)-6-propylbenzo[d]thiazol-2(3H)-one hydrochloride, HA171 (39)



39, HA171

[0226] A solution of 3-(2-bromoethyl)-6-propylbenzo[d] thiazol-2(3H)-one **3** (200 mg, 0.67 mmol, 1 equiv.) in NMP (2 mL), potassium carbonate (276.2 mg, 1.99 mmol, 3.0 equiv.) and (1s,4s)-7-azabicyclo[2.2.1]heptane (97.1 mg, 0.99 mmol, 1.5 equiv.) in NMP (2 mL) were added. The reaction mixture was stirred at 70 °C for 20h.Then, the reaction mixture was poured onto water, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with brine, dried with Na_2SO_4, filtered, and the solvent was evaporated *in vacuo*. The crude compound was purified by silica gel chromatography using a gradient of ethyl acetate and methanol to afford **39** (90 mg, 42.7%). HCl salt was prepared by dissolving the free base (90 mg, 0.28 mmol) in diethyl ether, then excess 2M HCl/diethyl ether (1.5 mL) was added. The reaction mixture was stirred for 48 h to yield the hydrochloride salt as a white solid (93.7 mg, combined yield 39.8%). **^{1}H NMR** (600 MHz, Methanol-d_4) δ 7.42 (d, J = 1.5 Hz, 1H), 7.31 (d, J = 8.3 Hz, 1H), 7.26 (dd, J = 8.3, 1.7 Hz, 1H), 4.41 (t, J = 6.2 Hz, 2H), 4.32 (p, J = 2.4 Hz, 2H), 3.47 (t, J = 6.2 Hz, 2H), 2.64 (t, J = 7.7 Hz, 2H), 2.20 – 2.13 (m, 2H), 2.11 – 2.03 (m, 2H), 1.86 (dt, J = 18.0, 6.6 Hz, 4H), 1.65 (hex, J = 7.4 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (JMOD,151 MHz, MeOD) δ 172.93, 140.21, 135.56, 128.43, 123.84, 123.77, 111.79, 65.80, 45.08, 40.00, 38.51, 28.23, 26.17, 25.87, 13.91. **NB**: Three carbons are overlapping. **UPLC/MS (Method B)**: t_R = 2.87 min, MS (ESI$^+$) 317.46 $(M+H)^+$. **HRMS (ESI) for $C_{18}H_{25}N_2OS^+$**: Theoretical $[M+H]^+$= 317.1682 (0.6 ppm); found 317.1684.

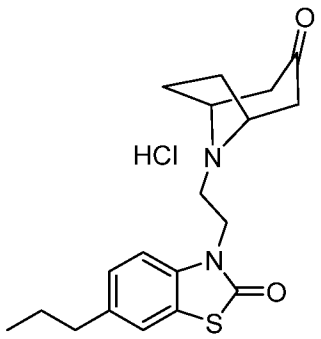
[0227] 3-(2-(8-azabicyclo[3.2.1]octan-8-yl)ethyl)-6-propylbenzo[d]thiazol-2(3H)-one hydrochloride, HA172 (40)



40, HA172

[0228] A solution of 3-(2-bromoethyl)-6-propylbenzo[d]thiazol-2(3H)-one **3** (200 mg, 0.67 mmol, 1 equiv.) in THF (2 mL) was added to a mixture of 8-azabicyclo[3.2.1]octane (111.1 mg, 0.99 mmol, 1.5 equiv.), and potassium carbonate (276 mg, 1.99 mmol, 3.0 equiv.) in THF (3 mL). The reaction mixture was refluxed for 16 h. After being cooled, the mixture was filtered, and the filtrate was evaporated. The residue was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **40** (169 mg, 77%). HCl salt was prepared by dissolving the free base (169 mg, 0.51 mmol) in DCM, then excess 4N HCl in dioxane (1.2 mL) was added. The reaction mixture was stirred for 24h to yield the hydrochloride salt as a white solid (140.6 mg, combined yield 57.5%). **^{1}H NMR** (600 MHz, Methanol-d_4) δ 7.43 (d, J = 1.6 Hz, 1H), 7.31 (d, J = 8.3 Hz, 1H), 7.26 (dd, J = 8.2, 1.7 Hz, 1H), 4.42 (t, J = 6.4 Hz, 2H), 4.22 – 4.15 (m, 2H), 3.41 – 3.33 (m, 2H), 2.64 (t, J = 7.7 Hz, 2H), 2.32 – 2.26 (m, 2H), 2.10 – 2.00 (m, 4H), 1.89 – 1.76 (m, 3H), 1.69 – 1.62 (m, 3H), 0.94 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (JMOD, 151 MHz, MeOD) δ 173.07, 140.21, 135.63, 128.43, 123.84, 123.81, 111.77, 64.85, 50.51, 38.82, 38.51, 30.72 (2C, confirmed by HSQC), 25.87, 25.05 (2C, confirmed by HSQC), 15.60, 13.90. **NB**: one carbon is overlapping. **UPLC/MS (Method B)**: t_R = 2.29 min, MS (ESI$^+$) 331.57 $(M+H)^+$. **HRMS (ESI) for $C_{19}H_{27}N_2OS^+$**: Theoretical $[M+H]^+$= 331.1839 (2.1 ppm); found 331.1832.

[0229] 3-(2-(3-oxo-8-azabicyclo[3.2.1]octan-8-yl)ethyl)-6-propylbenzo[d]thiazol-2(3H)-one hydrochloride, HA161 (41)

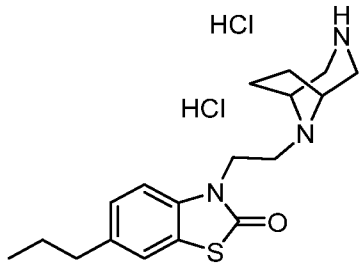


41, HA161

[0230] A solution of 3-(2-bromoethyl)-6-propylbenzo[d]thiazol-2(3H)-one **3** (200 mg, 0.67 mmol, 1 equiv.) in THF (2 mL) was added to a mixture of 8-azabicyclo[3.2.1]octan-3-one (125.1 mg, 0.99 mmol, 1.5 equiv.), and potassium carbonate (276 mg, 1.99 mmol, 3.0 equiv.) in THF (6 mL). The reaction mixture was heated at 55 °C for 48 h. After being cooled, the mixture was filtered, and the filtrate was evaporated. The residue was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **41** (124 mg, 54.4%). HCl salt was prepared by dissolving the free base (124 mg, 0.36 mmol) in DCM, then excess 4N HCl in dioxane (1.2 mL) was added. The reaction mixture was stirred for 48h. The solvents were removed by evaporation under reduced pressure and the salt was triturated with diethyl ether, then filtered to yield the hydrochloride salt as a pink solid (134 mg, combined yield 52.8%). **^{1}H NMR of the free base** (600 MHz, DMSO-d_6) δ 7.47 (d, J = 1.6 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.19 (dd, J = 8.3, 1.7 Hz, 1H), 4.08 (t, J = 6.6 Hz, 2H), 3.54 – 3.47 (m, 2H), 2.83 (t, J = 6.6 Hz, 2H), 2.57 (t, J = 7.5 Hz, 2H), 2.51- 2.49 (m, 2H), 2.02 – 1.98 (m, 2H), 1.93 – 1.83 (m, 2H), 1.59 (hex, J = 7.3 Hz, 2H), 1.48 – 1.37 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H). **^{13}C NMR of the free base** (JMOD, 151 MHz, DMSO) δ 209.01, 168.80, 137.17, 135.13, 126.70, 122.32, 121.28, 111.32, 58.48, 47.17, 47.14, 41.67, 36.75, 27.59, 24.24, 13.54. **^{1}H NMR of the salt** (600 MHz, Methanol-d_4) (Mixture of two conformers are overlapping), δ 7.44 – 7.38 (m, 3H), 7.36 – 7.30 (m, 1H), 7.29 – 7.23 (m, 2H), 4.56 – 4.51 (m, 4H), 4.43 (t, J = 6.1 Hz, 2H), 4.30 – 4.13 (m, 2H), 3.70 – 3.54 (m, 2H), 3.44 – 3.38 (m, 2H), 3.20 – 3.12 (m, 2H), 2.69 – 2.02 (m, 18H), 1.69 – 1.62 (m, 4H), 0.94 (m, 6H). **^{13}C NMR of the salt** (JMOD, 151 MHz, MeOD) δ 203.16, 173.15 (2C), 140.21 (2C), 135.60 (2C), 128.45 (2C), 123.79 (2C), 111.98 (2C), 63.83 (2C), 63.66 (2C), 50.42 (2C), 49.96, 47.43, 42.03, 40.28, 39.20 (2C), 38.50, 26.24, 25.84, 24.43 (2C), 13.92. **NB**: Spectrum represents a

mixture of two conformational isomers; i.e. seven carbon signals are missing due to overlap from the two isomers. **UPLC/MS (Method B)**: t_R = 2.63 min, MS (ESI+) *m/z* = 345.56 $[M+H]^+$. **HRMS (ESI) for $C_{19}H_{25}N_2O_2S^+$**: Theoretical $[M+H]^+$= 345.1631 (2.0 ppm); found 345.1624.

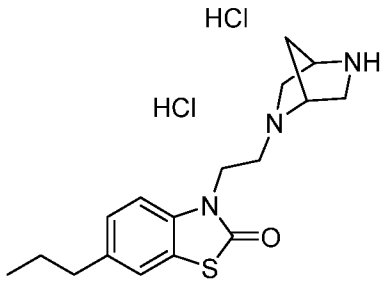
[0231] 3-(2-(3,8-diazabicyclo[3.2.1]octan-8-yl)ethyl)-6-propylbenzo[d]thiazol-2(3H)-one dihydrochloride, HA157 (42)



42, HA157

[0232] A solution of 3-(2-bromoethyl)-6-propylbenzo[d]thiazol-2(3H)-one **3** (200 mg, 0.67 mmol, 1 equiv.) in THF (2 mL) was added to a mixture of tert-butyl 3,8-diazabicyclo[3.2.1]-octane-3-carboxylate (212 mg, 0.99 mmol, 1.5 equiv.) and potassium carbonate (276 mg, 1.99 mmol, 3.0 equiv.) in THF (4 mL). The reaction mixture was heated at 55 °C for 40 h. After being cooled, the mixture was filtered, and the filtrate was evaporated. The residue was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **42** (258 mg, 89.7%). Boc group deprotection: To a solution of **42** (258 mg, 0.59 mmol) in DCM (2 mL), excess 4N HCl in dioxane (1.6 mL) was added. The reaction mixture was stirred for 48 h at room temperature. The solvents were removed by evaporation under reduced pressure and the residue was triturated with diethyl ether, then filtered to yield the dihydrochloride salt as a white solid (174 mg, combined yield 65%). **^{1}H NMR** (600 MHz, Methanol-d_4) δ 7.42 (d, *J* = 1.7 Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.26 (dd, *J* = 8.3, 1.7 Hz, 1H), 4.53 – 4.45 (m, 4H), 3.84 (d, *J* = 14.0 Hz, 2H), 3.60 (d, *J* = 14.1 Hz, 2H), 3.51 (t, *J* = 6.4 Hz, 2H), 2.64 (t, *J* = 7.5 Hz, 2H), 2.57 – 2.51 (m, 2H), 2.37 – 2.30 (m, 2H), 1.65 (hex, *J* = 7.4 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (JMOD, 151 MHz, MeOD) δ 173.26, 140.24, 135.57, 128.43, 123.82, 123.81, 111.94, 61.27, 49.75 (2 C, confirmed by HSQC), 47.14 (confirmed by HSQC), 38.76 (2 C, confirmed by HSQC), 38.52, 25.87, 23.61(2 C, confirmed by HSQC), 13.91. **UPLC/MS (Method B)**: t_R = 2.68 min, MS (ESI+) *m/z* = 332.54 $[M+H]^+$. **HRMS (ESI) for $C_{18}H_{26}N_3OS^+$**: Theoretical $[M+H]^+$= 332.1791 (0.9 ppm); found 332.1788.

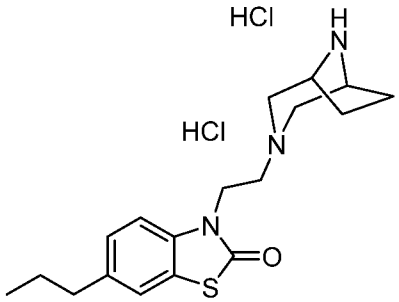
[0233] 3-(2-((1R,4R)-2,5-diazabicyclo[2.2.1]heptan-2-yl)ethyl)-6-propylbenzo[d]thiazol-2(3H)-one dihydrochloride, HA158 (43)



43, HA158

[0234] A solution of 3-(2-bromoethyl)-6-propylbenzo[d]thiazol-2(3H)-one **3** (200 mg, 0.67 mmol, 1.36 equiv.) in THF (2 mL) was added to a mixture of (1S,4S)-(−)-2-Boc-2,5-diazabicyclo-[2.2.1]heptane (98.1 mg, 0.49 mmol, 1 equiv.) and potassium carbonate (276 mg, 1.99 mmol, 4.0 equiv.) in THF (4 mL). The reaction mixture was heated at 55 °C for 24 h, then tetrabutylammonium iodide (123 mg, 0.33 mmol, 0.67 equiv.) was added and the reaction was heated at 55 °C for additional 24 h. After being cooled, the mixture was filtered, and the filtrate was evaporated. The residue was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **43** (162 mg, 78.4%). Boc group deprotection: To a solution of **43** (162 mg, 0.39 mmol) in DCM (2 mL), excess 4N HCl in dioxane (1 mL) was added. The reaction mixture was stirred for 48 h at room temperature. The solvents were removed by evaporation under reduced and the residue was triturated with diethyl ether, then filtered to yield the dihydrochloride salt as a pale yellow solid (123 mg, combined yield 63.7%). **^{1}H NMR** (600 MHz, Methanol-d_4) δ 7.42 (d, J = 1.5 Hz, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.26 (dd, J = 8.4, 1.6 Hz, 1H), 4.85 – 4.79 (m, 1H), 4.63 – 4.59 (m, 1H), 4.50 – 4.38 (m, 2H), 3.86 (dd, J = 13.5, 2.2 Hz, 1H), 3.78 – 3.62 (m, 4H), 3.60 (dd, J = 13.5, 2.8 Hz, 1H), 2.64 (t, J = 7.6 Hz, 2H), 2.58 (d, J = 13.3 Hz, 1H), 2.30 (d, J = 13.1 Hz, 1H), 1.65 (hex, J = 7.4 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (JMOD, 151 MHz, MeOD) δ 173.06, 140.25, 135.50, 128.43, 123.81, 123.75, 111.98, 64.42, 58.25, 57.23, 39.48, 38.52, 34.38 (confirmed by HSQC), 25.86, 13.91. **NB**: two carbons are overlapping. **UPLC/MS (Method B)**: t_R = 2.49 min, MS (ESI+) m/z = 318.54 $[M+H]^+$. **HRMS (ESI) for $C_{17}H_{24}N_3OS^+$**: Theoretical $[M+H]^+$ = 318.1635 (1.6 ppm); found 318.1640.

[0235] 3-(2-(3,8-diazabicyclo[3.2.1]octan-3-yl)ethyl)-6-propylbenzo[d]thiazol-2(3H)-one dihydrochloride, HA134/HA160 (44)

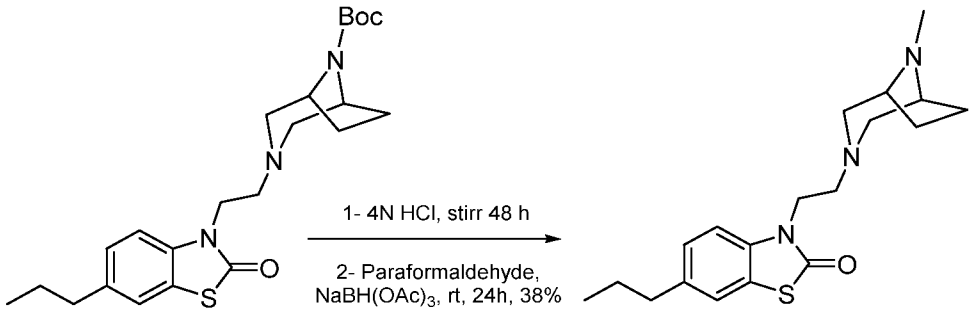


44, HA134/ HA160

[0236] A solution of 3-(2-bromoethyl)-6-propylbenzo[d]thiazol-2(3H)-one **3** (500 mg, 1.67 mmol, 1 equiv.) in THF (6 mL) was added to a mixture of tert-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (424 mg, 1.99 mmol, 1.2 equiv.), and potassium carbonate (690.5 mg, 4.99 mmol, 3.0 equiv.) in THF(4 mL). The reaction mixture was refluxed for 18 h. After being cooled, the mixture was filtered, and the filtrate was evaporated. The residue was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **44** (506 mg, 75%). Boc group deprotection: To a solution of **44** (506 mg, 1.17 mmol) in DCM (2 mL), excess 4N HCl in dioxane (3 mL) was added. The reaction mixture was stirred for 48 h at room temperature, the reaction was monitored by LCMS for complete deprotection. Then, the solvents were removed by evaporation under reduced and the residue was triturated with diethyl ether, then filtered to yield the dihydrochloride salt as a white solid (476 mg, combined yield 70.6%). Free basing of the salt: The hydrochloric salt form of **44** (476 mg, mmol) was stirred in a saturated $NaHCO_3$ solution for 2 h, followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford the free base **44** (330 mg, combined yield 60%). Conversion to oxalate salt: To a solution of the free base **44** (200 mg, 0.60 mmol, 1 equiv.) in diethyl ether, a solution of oxalic acid (109 mg, 1.2 mmol, 2 equiv.) in diethyl ether was added. The reaction mixture was left to stir for 3 days, then the solvent was evaporated under reduced pressure, and the residue was crystalized from ethanol (165 mg, 82.5%). **^{1}H NMR of HCl salt** (600 MHz, Methanol-d_4) δ 7.41 (d, J = 8.2 Hz, 1H), 7.39 (d, J = 1.5 Hz, 1H), 7.23 (dd, J = 8.2, 1.7 Hz, 1H), 4.45 (t, J = 6.3 Hz, 2H), 4.37 – 4.30 (m, 2H), 3.89 – 3.81 (m, 2H), 3.59

– 3.51 (m, 2H), 3.46 (t, J = 6.5 Hz, 2H), 2.62 (t, J = 7.5 Hz, 2H), 2.47 – 2.39 (m, 2H), 2.29 – 2.22 (m, 2H), 1.64 (hex, J = 7.3 Hz, 2H), 0.93 (t, J = 7.4 Hz, 3H). **^{13}C NMR of HCl salt** (JMOD, 151 MHz, MeOD) δ 172.97, 140.13, 135.61, 128.40, 123.72, 123.62, 112.23, 55.93, 55.75, 55.23, 38.57, 38.50, 25.85, 25.39, 13.93. **NB**: three carbons are overlapping. **UPLC/MS (Method B)**: t_R = 3.12 min, MS (ESI+) 332.40 $(M+H)^+$. **HRMS (ESI) for $C_{18}H_{26}N_3OS^+$**: Theoretical $[M+H]^+$= 332.1791 (3.6 ppm); found 332.1779.

[0237] ***Scheme 1B: Methylation of 44 (HA134) and synthesis of 47 (HA204).***



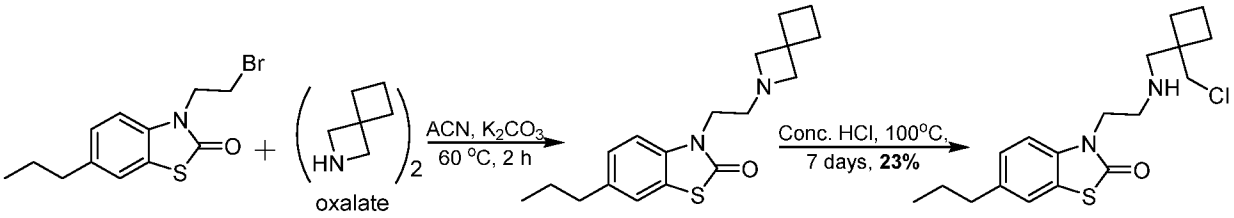
44, HA134 **47, HA204**

[0238] The synthesis of analog **47** started from the deprotection of the boc group of analog **44** using HCl in dioxane followed by basic workup, which resulted in the *N*-deprotected free base. *N*-methylation was carried out through reductive amination reaction using paraformaldehyde and Sodium triacetoxyborohydride, $NaBH(OAc)_3$, to afford **47** in 38% yield, Scheme 1B.

[0239] Method: $NaBH(OAc)_3$ (128.67 mg, 0.59 mmol) was added to a stirring solution of the Boc deprotected free base of **44** (122 mg, 0.37 mmol) and paraformaldehyde (33.16 mg, 0.37 mmol) in dichloroethane (3 mL), and the reaction mixture was left to stir at room temperature overnight. The reaction was quenched with a saturated $NaHCO_3$ solution, and the aqueous phase was extracted with DCM. The combined organic extract was washed with brine, dried with Na_2SO_4, filtered, and the solvent was evaporated *in vacuo*. The crude compound was purified by alumina column chromatography using a gradient of ethyl acetate and methanol to afford **47** (48 mg, 37.8% yield). To a solution of the **47** (48 mg, 0.14 mmol, 1 equiv.) in diethyl ether, a solution of oxalic acid (25 mg, 0.27 mmol, 2 equiv.) in diethyl ether was added. The reaction mixture was left to stir overnight, then the salt was triturated with diethyl ether, and filtered to give the dioxalate salt of **47** (60 mg, combined yield 31%). **^{1}H NMR** (600 MHz, Methanol-d_4) δ 7.39 (d, J = 1.3 Hz, 1H), 7.23 – 7.19 (m, 2H), 4.13 (t, J = 5.8 Hz, 2H), 3.82 – 3.78 (m, 2H), 2.95

(d, J = 12.3 Hz, 2H), 2.80 (t, J = 5.8 Hz, 2H), 2.74 (s, 3H), 2.65 – 2.56 (m, 4H), 2.08 – 1.97 (m, 4H), 1.66 (hex, J = 7.4 Hz, 2H), 0.95 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (JMOD, 151 MHz, MeOD) δ 172.30, 164.13, 139.66, 136.15, 128.14, 123.58, 123.46, 112.18, 65.25, 57.32, 54.00, 40.62, 39.26, 38.54, 25.90, 24.59, 13.97. **NB**: three carbons are overlapping. **UPLC/MS (Method B)**: t_R = 2.92 min, MS (ESI+) 346.37 $(M+H)^+$. **HRMS (ESI) for $C_{19}H_{28}N_3OS^+$**: Theoretical $[M+H]^+$= 346.1948 (4.6 ppm); found 346.1964.

[0240] ***Scheme 1C. Acid hydrolysis of analog 33 to synthesize analog 48.***



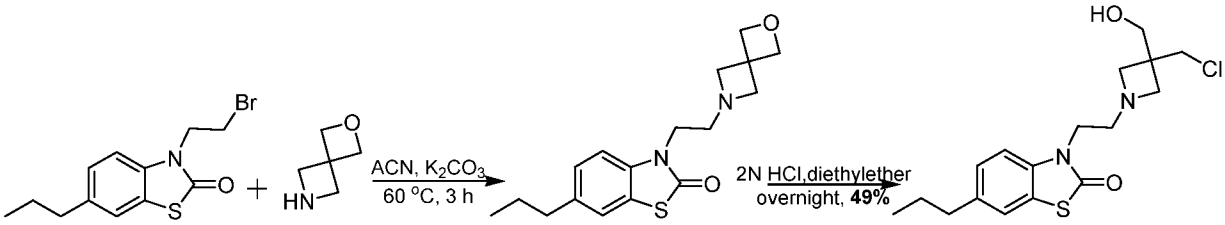
3 **33** **48, HA98**

[0241] To compare the effect of the spirocyclic derivative to its open ring counterpart on affinity and metabolism, an attempt was made to open the ring of analog **33**. When the reaction was treated with 4N HCl in dioxane for two days, the reaction did not proceed to completion and a small conversion was detected by LCMS. Harsh conditions were needed to open the ring and have complete conversion. So, analog **33** was heated at 100°C in conc. HCl for 7 days. This led to a nucleophilic attack of the chloride anion on the carbon alpha to the protonated nitrogen and the opening of the strained azetidine ring that afforded analog **48**. The reaction was monitored and confirmed by LCMS. A side product with the mass correspond to the opening of the cyclobutane ring with two chlorine atoms was also detected by LCMS. After completion of the reaction, the requisite free base **48** was obtained after neutralization with $NaHCO_3$ solution, extraction with dichloromethane (DCM), and column purification. Then, the oxalate salt was created, Scheme 1C.

[0242] **Method**: To a solution of **33** (125 mg, 0.3950 mmol) in diethyl ether, 2N HCl in diethyl ether (1 mL) was added. The reaction was stirred for 24 h, small conversion was detected by LCMS. Concentrated hydrochloric acid solution (2mL) was added and the reaction was left to stir for 24 h at room temperature, reaction was monitored by LCMS. Then, 3 mL of concentrated hydrochloric acid solution was added to the mixture and the reaction was stirred at 100°C for 7 days. The reaction was monitored and confirmed by LCMS for complete conversion. The

reaction mixture was neutralized with a saturated $NaHCO_3$ solution, followed by extraction of the aqueous layer by DCM. The crude compound (88 mg) was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to give **48** (45 mg, 23%). To a solution of the **48** (45 mg, 0.13 mmol, 1 equiv.) in DCM, a solution of oxalic acid (11.5 mg, 0.13 mmol, 1 equiv.) in diethyl ether was added. The reaction mixture was left to stir overnight, then the salt was triturated with diethyl ether, and filtered to give the oxalate salt of **48** (38.7 mg, combined yield 22.1%). **^{1}H NMR of the salt** (600 MHz, DMSO-d_6) δ 7.51 (d, J = 1.6 Hz, 1H), 7.37 (d, J = 8.3 Hz, 1H), 7.22 (dd, J = 8.3, 1.8 Hz, 1H), 4.21 (t, J = 7.2 Hz, 2H), 3.84 (s, 2H), 3.15 (t, J = 7.2 Hz, 2H), 3.08 (s, 2H), 2.58 (t, J = 7.5 Hz, 2H), 2.01 – 1.78 (m, 6H), 1.59 (hex, J = 7.4 Hz, 2H), 0.88 (t, J = 7.3 Hz, 3H). **^{13}C NMR of the salt** (JMOD, 151 MHz, DMSO) δ 169.15, 163.86, 137.59, 134.61, 126.83, 122.50, 121.46, 111.13, 51.85, 50.41, 45.33, 41.63, 39.00, 36.75, 27.16 (2C, confirmed by HSQC), 24.30, 13.99, 13.51. **UPLC/MS (Method A)**: t_R = 3.19 min, MS (ESI+) 353.25 $(M+H)^+$. **HRMS (ESI) for $C_{18}H_{26}ClN_2OS^+$**: Theoretical $[M+H]^+$= 353.1449 (4.2 ppm); found 353.1464.

[0243] ***Scheme 1D. Acid hydrolysis of analog 34 to get the open ring analog 49.***



6 **34** **49, HA106**

[0244] The synthesis of **49,** the open ring counterpart of analog **34,** was also obtained in a similar way to the previous scheme, Scheme 1D. However, less harsh conditions were used and were enough to open the oxetane ring using 2N HCl/ ether at room temperature and the reaction was left for only 24h, checked for completion by LCMS. No side products were formed, and the final derivative was tested as a hydrochloric salt. The ^{1}H NMR of the salt showed a mixture of diastereomers.

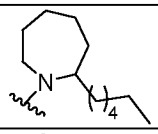
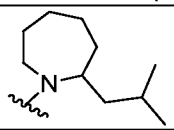
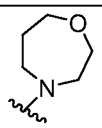
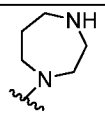
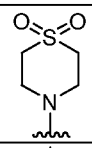
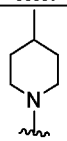
[0245] Method: To a solution of **34** (91 mg, 0.2858 mmol) in diethyl ether, 2N HCl in diethyl ether (1 mL) was added. The reaction mixture was left to stir for 24 h and monitored by LCMS for complete conversion. The solvent was evaporated *in vacuo*, and the residue was triturated

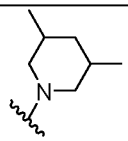
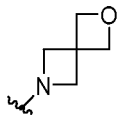
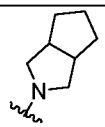
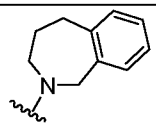
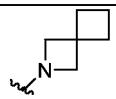
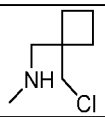
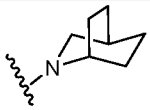
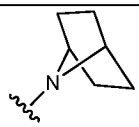
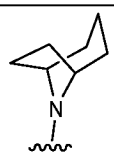
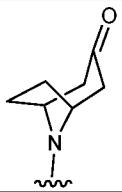
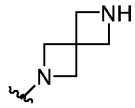
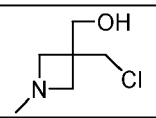
with diethyl ether, and filtered to give the hydrochloride salt of **49** as a white solid (80 mg, 49%). **^{1}H NMR** (600 MHz, DMSO-d_6) (mixture of diastereomers are overlapping), δ 11.35 (br s, 1H), 11.02 (br s, 1H), 7.51 (d, J = 1.8 Hz, 2H), 7.40 (d, J = 8.3 Hz, 2H), 7.21 (dd, J = 8.2, 1.7 Hz, 2H), 5.55 (br s, 2H), 4.21 (t, J = 5.8 Hz, 4H), 4.07 – 3.79 (m, 12H), 3.68 (s, 2H), 3.60 – 3.44 (m, 6H), 2.58 (t, J = 7.6 Hz, 4H), 1.59 (hex, J = 7.4 Hz, 4H), 0.88 (t, J = 7.3 Hz, 6H). **^{13}C NMR** (JMOD, 151 MHz, DMSO) δ 169.43, 137.65, 134.33 (2C), 126.76, 122.50, 121.60 (2C), 111.16, 60.71 (2C), 57.83, 56.91, 51.14, 50.35, 46.51, 46.14, 40.84, 40.21, 37.49, 36.74, 24.27, 13.51. **NB**: Spectrum represents a mixture of two diastereomers; i.e. eleven carbon signals are missing due to overlap from the two isomers. **UPLC/MS (Method A)**: t_R = 3.84 min, MS (ESI+) 355.37 $(M+H)^+$. **HRMS (ESI) for $C_{17}H_{24}ClN_2O_2S^+$**: Theoretical $[M+H]^+$= 355.1242 (2.0ppm); found 355.1249.

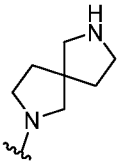
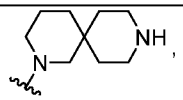
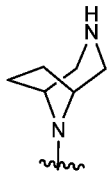
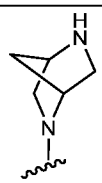
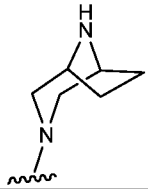
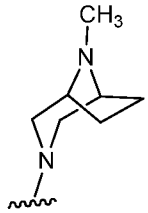
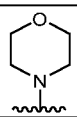
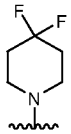
Metabolic Stability

[0246] Metabolic stability studies on compounds of Formula (I) were carried out as described above.

[0247] Table 1A: *In vitro* metabolic stability

Comp.	Compound code	R^{2A}	$t_{½}$ (min)	Cl int (µl/min/mg)
24	HA121		2.6	262.4
25	HA126		0.8	837.2
26	HA70		1.1	620.8
27	HA188		**6.9**	101.1
28	HA143		0.6	1114.9
29	HA71		0.9	772.8

Comp.	Compound code	R^{2A}	$t_{1/2}$ (min)	Cl_{int} (µl/min/mg)
30	MH-S3		0.9	743.4
34	HA109		0.9	763.2
31	MH-S4 /HA201		1.0	707.9
32	MH-S7		0.6	1112.2
33	HA111		1.1	652.2
48	HA98		0.8	885
38	HA170		0.9	744.5
39	HA171		0.8	831.5
40	HA172		0.9	808.2
41	HA161		0.5	1514
35	HA135		**>30**	2
49	HA106		1.0	679.8

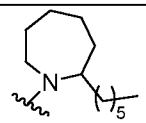
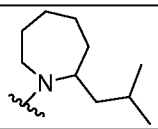
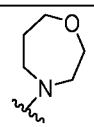
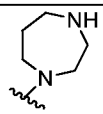
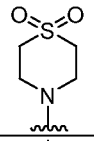
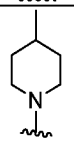
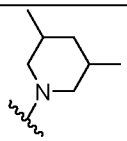
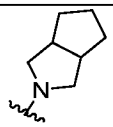
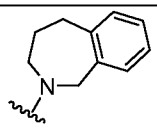
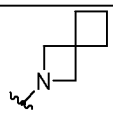
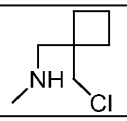
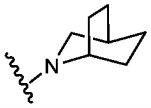
Comp.	Compound code	R^{2A}	$t_{1/2}$ (min)	Cl int (µl/min/mg)
36	HA99		**8.1**	85.2
37	MH-S6		2.3	306.5
42	HA157		**5.6**	123.7
43	HA158		**>30**	20.7
44	HA134		**>30**	11.8
47	HA204		**15.0**	46.1
45	**MCI174**		0.8	824.1
46	**MCI183**		**1.4**	489.3

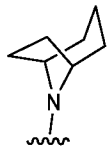
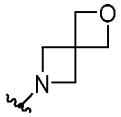
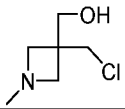
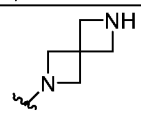
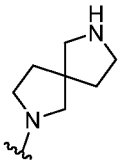
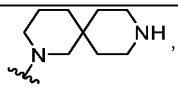
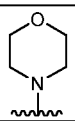
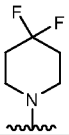
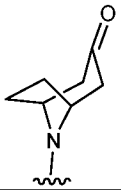
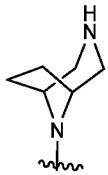
Binding Affinity

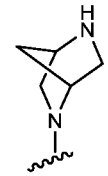
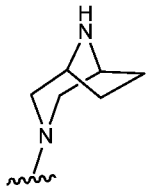
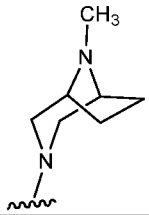
[0248] Binding affinity studies on compounds of Formula (I) were carried out as described above.

[0249] Data represent mean ± SD from triplicate assays, a: data from one assay, NT; not tested

[0250] Table 1B: *In vitro* binding affinity

#	Comp code	R^{2A}	K_i (nM ± SD)		K_i σ_2/ K_i σ_1
			σ_1R	σ_2R	
24	HA121		47.31 ± 0.86	259.70 ± 38.78	-
25	HA126		89.24 ± 59.78	239.79 ± 5.23	9
26	HA70		3.49 ± 0.91	ND	
27	HA188		17.83 ± 9.61	IC50 >1000	-
28	HA143		>1000	>1000	-
29	HA71		1.22 ± 0.17	533.86[a]	437.59
30	MH-S3		42.56 ± 5.61	1960.79 [a]	48.89
31	MH-S4 /HA201		8.37 ±1.58	[a]	94
32	MH-S7		154.19 ± 45.33	173.63 ± 66.63	0.94
33	HA111		4.12 ± 2.93	200.22 ± 26.39	-
48	HA98		39.46 ± 20.24	193.94 ± 71.55	-
38	HA170		2.63 ± 0.71	43.99 ± 0.03	-

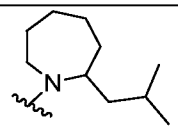
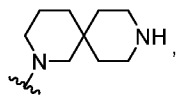
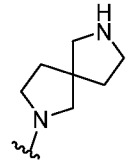
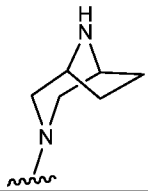
#	Comp code	R^{2A}	K_i (nM ± SD)		K_i σ2/ K_i σ1
			σ1R	σ2R	
39	HA171		11.97 ± 2.22	IC50 >1000	-
40	HA172		5.09 ± 1.05	38.93 ± 9.43	-
34	HA109		7.24 ± 1.01	2.09 ± 1.02	-
49	HA106		3.16 ± 0.04	36.81 ± 4.93	-
35	HA135		>1000	>1000 DEGRADES	-
36	HA99		73.67 ± 16.42	111.69 ± 29.51	0.74
37	MHS-6		192.88 ± 18.94	290.56 ± 28.52	1.5
45	MCI 174		9.89 ± 1.44	18.10 ± 1.58	
46	MCI 183		1.54 ± 0.84	62.91 ± 9.56	
41	HA161		1.44 ± 0.89	169.82 ± 129.36	-
42	HA157		8.69 ± 2.63	178.30 ± 55.92	27

#	Comp code	R^{2A}	K_i (nM ± SD)		K_i σ2/ K_i σ1
			σ1R	σ2R	
43	HA158		185.61 ± 139.22	259.12 ± 34.32	1.5
44	HA134		13.66 ± 9.97	115.36 ± 83.94	0.045
47	HA204		57.20 ± 7.25	103.16 ± 24.28	-

Permeability

[0251] Permeability studies on compounds of Formula (I) were carried out as described above.

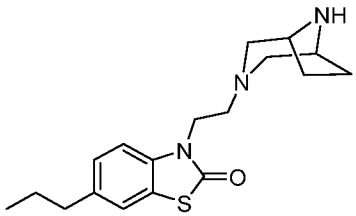
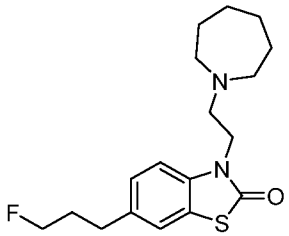
[0252] Table 1C: In vitro permeability

Comp numb	Comp code	R	Caco-2 Permeability (P_{app}, 10^{-6} cm/sec)	Permeability Class
25	HA126		0.08 ± 0.03	Low
37	MH-S6		1.37 ± 0.29	Low
36	HA99		4.23 ± 1.04	Moderate
44	HA134		4.77 ± 0.31	Moderate

In vivo PK Parameters for HA134, CM304

[0253] Permeability studies on compounds of Formula (I) were carried out as described above.

[0254] Table 1D: *In vivo* PK parameters of HA134 and CM304 in CD-1 mice.

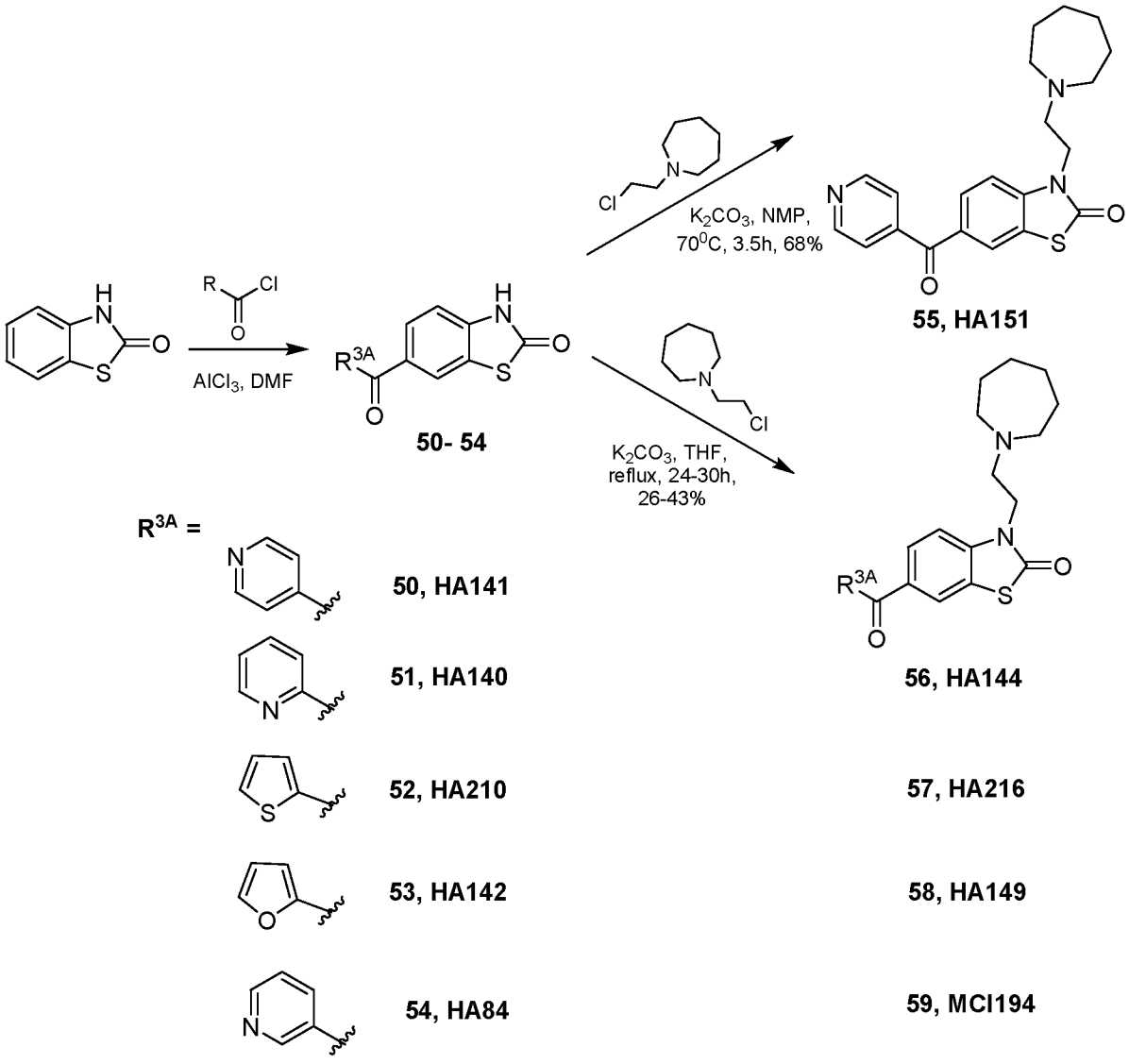
PK parameters	 HA134		 CM304	
	IV (2.5 mg/Kg)	PO (50 mg/Kg)	IV (2.5 mg/Kg)	PO (50 mg/Kg)
C_{max} (µg/L)	-	567.6	-	103.6
T_{max} (h)	-	0.5	-	0.1
Half-life (h)	2.0	3.5	1.0	1.8
Cl_{obs} or Cl_{obs_F} (L/h/Kg)	8.4	20.9	7.6	742.7
Bioavailability (% F)	-	34.8	-	1.0
Brain to Plasma (AUC_{last} ratio)	2.3	1.9	4.2	3.1

Compounds of Formula (II)

Synthesis

[0255] The below scheme exemplifies the synthetic route utilized to prepare compounds of Formula (II).

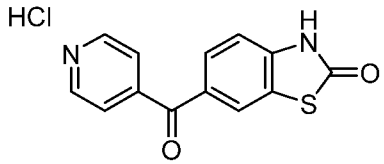
[0256] Scheme 2A: Synthesis of Compounds of Formula (II)



[0257] General procedure D: Synthesis of 6-heteroaromatic benzothiazolone derivatives (50-54). Anhydrous DMF was added dropwise to $AlCl_3$ and stirred for 30 min at 45 °C. 2(*3H*)-benzothiazolone was added portion wise and followed by the addition of the corresponding acid chloride. Then, the mixture was heated at the specified temperature for a specified time and

monitored by TLC/MS, after which the reaction mixture was poured onto ice/H_2O and stirred overnight, then filtered and dried in the oven.

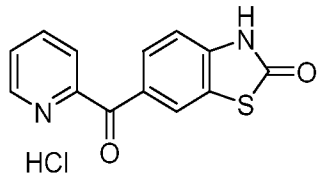
[0258] ***6-isonicotinoylbenzo[d]thiazol-2(3H)-one, HA141 (50)***



50, HA141

[0259] Anhydrous DMF (3.5 mL) was added dropwise to $AlCl_3$ (1940 mg, 145.51 mmol, 11 equiv.) and stirred for 30 min at 45 °C. Benzothiazolone (2000 mg, 13.23 mmol, 1 equiv.) was added portion wise and followed by the addition of isonicotinoyl chloride hydrochloride (2590 mg, 14.55 mmol, 1.1 equiv.). Then, the mixture was heated at 130 °C for 4 h, after which the reaction mixture was poured onto ice/H_2O and stirred overnight. The crude product was collected by filtration, washed with cold ethanol and oven dried (2942 mg, 76%). The crude was used for the next step without further purification. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 13.21 (s, 1H), 9.64 – 9.61 (m, 2H), 8.90 (d, J = 1.8 Hz, 1H), 8.54 (dd, J = 8.3, 1.8 Hz, 1H), 8.44 – 8.42 (m, 2H), 8.08 (d, J = 8.4 Hz, 1H). **TLC/MS** (ESI+): 257.113 $(M+H)^+$. **UPLC/MS (Method A)**: t_R = 2.59 min, MS (ESI+) 257.22 $(M+H)^+$.

[0260] ***6-picolinoylbenzo[d]thiazol-2(3H)-one, HA140 (51)***

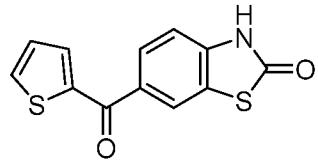


51, HA140

[0261] Anhydrous DMF (3.5 mL) was added dropwise to $AlCl_3$ (1940 mg, 145.51 mmol, 11 equiv.) and stirred for 30 min at 45 °C. Benzothiazolone (2000 mg, 13.23 mmol, 1 equiv.) was added portion wise and followed by the addition of picolinoyl chloride hydrochloride (2590 mg, 14.55 mmol, 1.1 equiv.). Then, the mixture was heated at 130 °C for 30 h, after which the reaction mixture was poured on ice/H_2O and stirred overnight. The crude product was collected by filtration (2284 g, yield as crude 59%). The crude was used for the next step without further

purification. **^{1}H NMR** (600 MHz, Methanol-d_4) δ 8.68 (dt, J = 4.8, 1.3 Hz, 1H), 8.19 (d, J = 1.6 Hz, 1H), 8.03 (td, J = 7.7, 1.7 Hz, 1H), 7.99 – 7.94 (m, 2H), 7.62 (ddd, J = 7.5, 4.8, 1.3 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H). **UPLC/MS (Method A)**: t_R = 3.06 min, MS (ESI+) 257.37 $(M+H)^+$.

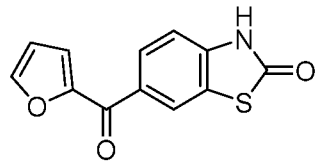
[0262] ***6-(thiophene-2-carbonyl)benzo[d]thiazol-2(3H)-one, HA210 (52)***



52, HA210

[0263] Anhydrous DMF (3.5 mL) was added dropwise to $AlCl_3$ (5820 mg, 43.65 mmol, 11 equiv.) and stirred for 30 min at 45 °C. Benzothiazolone (600 mg, 3.9 mmol, 1 equiv.) was added portion wise and followed by the addition of thiophene-2-carbonyl chloride (0.46 mL, 14.36 mmol, 1.1 equiv.). Then, the mixture was heated at 85 °C for 22 h, after which the reaction mixture was poured onto ice/H_2O and stirred overnight. The crude product was collected by filtration, washed with cold ethanol and oven dried. The crude was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **52** as a white solid (246 mg, 24%). **^{1}H NMR** (600 MHz, Acetone-d_6) δ 8.13 (d, J = 1.8 Hz, 1H), 7.98 (dd, J = 5.0, 1.1 Hz, 1H), 7.87 (dd, J = 8.3, 1.8 Hz, 1H), 7.79 (dd, J = 3.7, 1.1 Hz, 1H), 7.38 (d, J = 8.3 Hz, 1H), 7.28 (dd, J = 5.0, 3.8 Hz, 1H). **^{13}C NMR** (JMOD, 151 MHz, Acetone) δ 186.57, 170.84, 144.28, 140.74, 135.50, 135.17, 133.61, 129.15, 129.00, 125.12, 124.89, 112.03. **UPLC/MS (Method A)**: t_R = 1.87 min, MS (ESI+) 262.10 $(M+H)^+$.

[0264] ***6-(furan-2-carbonyl)benzo[d]thiazol-2(3H)-one, HA142 (53)***

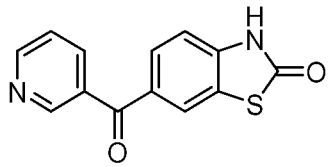


53, HA142

[0265] Anhydrous DMF (3.5 mL) was added dropwise to $AlCl_3$ (1940 mg, 145.51 mmol, 11 equiv.) and stirred for 30 min at 45 °C. 2(*3H*)-Benzothiazolone (2000 mg, 13.23 mmol, 1 equiv.) was added portion wise and followed by the addition of furan-2-carbonyl chloride (1.4 mL, 14.55

mmol, 1.1 equiv.). Then, the mixture was heated at 100 °C for 16 h, after which the reaction mixture was poured onto ice/H_2O and stirred overnight. The crude product was collected by filtration, washed with cold ethanol and oven dried. The crude was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **53** (1215 mg, 37.5%). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 12.28 (s, 1H), 8.22 (d, J = 2.0 Hz, 1H), 8.12 – 8.09 (m, 1H), 7.89 (dd, J = 8.3, 2.0 Hz, 1H), 7.42 (d, J = 3.5 Hz, 1H), 7.25 (dd, J = 8.4, 1.8 Hz, 1H), 6.79 (dd, J = 3.7, 1.9 Hz, 1H). **^{13}C NMR** (JMOD, 151 MHz, DMSO) δ 179.88, 170.52, 151.30, 148.32, 140.19, 131.18, 128.12, 124.19, 123.80, 120.93, 112.68, 111.31. **TLC/MS** (ESI+): 246.03 $(M+H)^+$.

[0266] ***6-nicotinoylbenzo[d]thiazol-2(3H)-one, HA84 (54)***



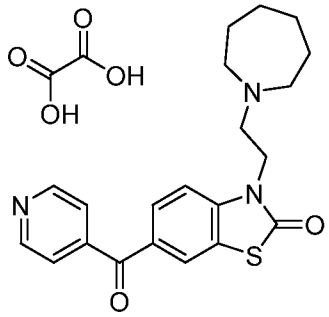
54, HA84

[0267] Anhydrous DMF (5 mL) was added dropwise to $AlCl_3$ (10 g, 72.75 mmol, 11 equiv.) and stirred for 30 min at 45 °C. Benzothiazolone (1 g, 6.61 mmol, 1 equiv.) was added portion wise and followed by the addition of nicotinoyl chloride (1.03 g, 7.27 mmol, 1.1 equiv.). Then, the mixture was heated at 100 °C for 46 h, after which the reaction mixture was poured onto ice/H_2O and stirred for 2 h. The crude product was collected by filtration, washed with cold ethanol and oven dried. The crude was purified by crystallization from ethanol to afford **54** (0.76 g, 45%) as pale yellow solid. **^{1}H NMR** (600 MHz, DMSO-d6) δ 12.37 (s, 1H), 8.91 (d, J = 2.1 Hz, 1H), 8.86 (dd, J = 4.9, 1.7 Hz, 1H), 8.17 (dt, J = 7.8, 2.0 Hz, 1H), 8.12 (d, J = 1.7 Hz, 1H), 7.75 (dd, J = 8.4, 1.8 Hz, 1H), 7.66 (dd, J = 7.9, 4.9 Hz, 1H), 7.28 (d, J = 8.3 Hz, 1H). **^{13}C NMR** (JMOD,151 MHz, DMSO) δ 193.23, 171.16, 152.45, 149.78, 141.32, 138.28, 134.04, 131.25, 129.71, 125.80, 124.60, 124.54, 111.97. **UPLC/MS (Method A)**: t_R = 2.32 min, MS (ESI^+) 257.23 $(M+H)^+$.

[0268] General procedure E: Synthesis of the final compounds (55-59) with different heteroaromatic rings at 6-position and azepane as a headgroup. The corresponding 6-

substituted benzothiazolone derivatives **(50-54)** were dissolved in the appropriate solvent, then a solution of 1-(2-chloroethyl) azepane hydrochloride and solid potassium carbonate were added.

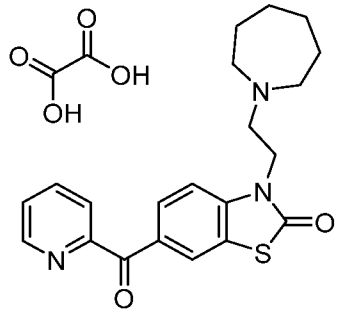
[0269] ***3-(2-(azepan-1-yl)ethyl)-6-isonicotinoylbenzo[d]thiazol-2(3H)-one oxalate, HA151 (55)***



55, HA151

[0270] To a solution of **50** (200 mg, 0.68 mmol, 1 equiv.) in NMP (3 mL), 1-(2-chloroethyl) azepane hydrochloride (185.55 mg, 0.94 mmol, 1.37 equiv.), and potassium carbonate (323 mg, 2.33 mmol, 3.4 equiv.) were added. The reaction mixture was heated at 70 °C for 3.5 h. After cooling, the reaction mixture was poured onto water, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and the solvent was evaporated *in vacuo*. The crude compound was purified by silica gel chromatography using a gradient of DCM and methanol to afford **55** (178 mg, 68%). To a solution of the **55** (132 mg, 0.34 mmol, 1 equiv.) in diethyl ether, a solution of oxalic acid (31.2 mg, 0.34 mmol, 1 equiv.) in diethyl ether was added. The reaction mixture was left to stir overnight, then the salt was triturated with diethyl ether, and filtered to give the oxalate salt of **55** as a white solid (126 mg, 77%). **^{1}H NMR** (600 MHz, Methanol-d_4) δ 8.78 – 8.76 (m, 2H), 8.06 (d, J = 1.7 Hz, 1H), 7.87 (dd, J = 8.4, 1.8 Hz, 1H), 7.70 – 7.65 (m, 2H), 7.52 (d, J = 8.5 Hz, 1H), 4.49 (t, J = 6.8 Hz, 2H), 3.57 (t, J = 6.8 Hz, 2H), 3.53 – 3.46 (m, 4H), 1.95 (p, J = 5.6 Hz, 4H), 1.75 (p, J = 2.8 Hz, 4H). **^{13}C NMR** (JMOD, 151 MHz, MeOD) δ 194.55, 172.37, 166.38, 150.94, 146.77, 141.95, 132.59, 130.80, 126.30, 124.50, 124.43, 112.10, 56.38, 54.74, 39.06, 27.41, 24.65. **NB**: five carbons are overlapping. **HRMS (ESI) for $C_{21}H_{24}N_3O_2S^+$**: Theoretical [M+H]+= 382.1594 (4.2 ppm); found 382.1600.

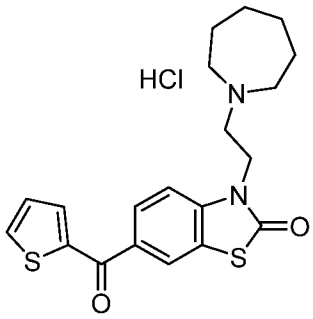
[0271] ***3-(2-(azepan-1-yl)ethyl)-6-picolinoylbenzo[d]thiazol-2(3H)-one oxalate, HA144 (56)***



56, HA144

[0272] To a solution of **51** (200 mg, 0.68 mmol, 1 equiv.) in THF (6 mL), 1-(2-chloroethyl) azepane hydrochloride (185.55 mg, 0.94 mmol, 1.37 equiv.), and potassium carbonate (323 mg, 2.33 mmol, 3.4 equiv.) were added. The reaction mixture was refluxed for 24 h. After being cooled, the mixture was filtered, and the filtrate was evaporated. The crude was purified by silica gel chromatography using a gradient of ethyl acetate and methanol to afford **56** (100 mg, 33.6%). To a solution of the **56** (54 mg, 0.14 mmol, 1 equiv.) in DCM, a solution of oxalic acid (12.6 mg, 0.14 mmol, 1 equiv.) in diethyl ether was added. The reaction mixture was left to stir overnight, then the salt was triturated with diethyl ether, and filtered to give the oxalate salt of **56** as a buff solid (30 mg, 45%). **^{1}H NMR** (600 MHz, Methanol-d_4) δ 8.71 – 8.68 (m, 1H), 8.32 (d, J = 1.7 Hz, 1H), 8.13 (dd, J = 8.5, 1.8 Hz, 1H), 8.06 (td, J = 7.7, 1.7 Hz, 1H), 8.03 – 7.99 (m, 1H), 7.65 (ddd, J = 7.5, 4.8, 1.3 Hz, 1H), 7.49 (d, J = 8.6 Hz, 1H), 4.49 (t, J = 6.7 Hz, 2H), 3.58 (t, J = 6.7 Hz, 2H), 3.54 – 3.44 (m, 4H), 1.96 (p, J = 5.4 Hz, 4H), 1.76 (p, J = 2.8 Hz, 4H). **^{13}C NMR** (JMOD, 151 MHz, MeOD) δ 193.11, 172.66, 166.47, 156.17, 149.65, 141.37, 139.05, 133.17, 131.52, 127.93, 127.22, 125.83, 123.83, 111.58, 56.49, 55.04, 39.03, 27.32, 24.77. **NB**: three carbons are overlapping. **HRMS (ESI) for $C_{21}H_{23}N_3O_2S^+$**: Theoretical $[M+H]^+$= 382.1584 (3.4 ppm); found 382.1597

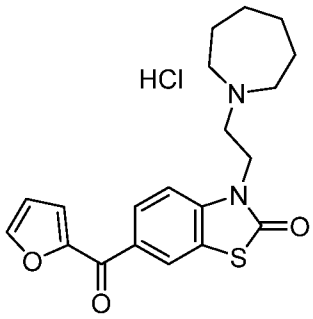
[0273] ***3-(2-(azepan-1-yl)ethyl)-6-(thiophene-2-carbonyl)benzo[d]thiazol-2(3H)-one hydrochloride, HA216 (57)***



57, HA216

[0274] To a solution of **52** (200 mg, 0.76 mmol, 1 equiv.) in THF (6 mL), 1-(2-chloroethyl) azepane hydrochloride (181.97 mg, 0.92 mmol, 1.2 equiv.), and potassium carbonate (317.3 mg, 2.29 mmol, 3 equiv.) were added. The reaction mixture was refluxed for 30 h. After being cooled, the mixture was filtered, and the filtrate was evaporated. The crude compound was purified firstly by silica gel chromatography using a gradient of ethyl acetate and methanol, then repurified by preparative thin layer chromatography (prep-TLC) using ethyl acetate: methanol (9:1) as eluent to afford **57** (128 mg, 43%). To a solution of **57** (128 mg, 0.33 mmol) in DCM (2 mL), excess 2N HCl in diethyl ether (1.4 mL) was added. The reaction mixture was stirred overnight at room temperature. Then, the solvents were removed by evaporation *in vacuo* and the residue was triturated with diethyl ether, then filtered to yield the hydrochloride salt of **57** as a white solid (135 mg, combined yield 41.7%). **^{1}H NMR** (600 MHz, Methanol-d_4) δ 8.15 (d, J = 1.7 Hz, 1H), 7.99 – 7.94 (m, 2H), 7.75 (dd, J = 3.8, 1.1 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.27 (dd, J = 4.9, 3.8 Hz, 1H), 4.53 (t, J = 6.6 Hz, 2H), 3.72 – 3.63 (m, 2H), 3.60 (t, J = 6.6 Hz, 2H), 3.40 – 3.32 (m, 2H), 2.07 – 1.89 (m, 4H), 1.83 – 1.70 (m, 4H). **^{13}C NMR** (JMOD, 151 MHz, MeOD) δ 188.03, 172.69, 144.13, 140.95, 136.45, 136.19, 134.96, 129.68, 129.48, 125.44, 124.40, 111.87, 56.55, 55.22, 39.04, 27.19, 24.87. **NB**: three carbons are overlapping. **UPLC/MS (Method B)**: t_R = 2.23 min, MS (ESI+) 387.34 $(M+H)^+$. **HRMS (ESI) for $C_{20}H_{24}ClN_2O_2S_2^+$**: Theoretical $[M+H]^+$= 387.1195 (3.9 ppm); found 387.1210.

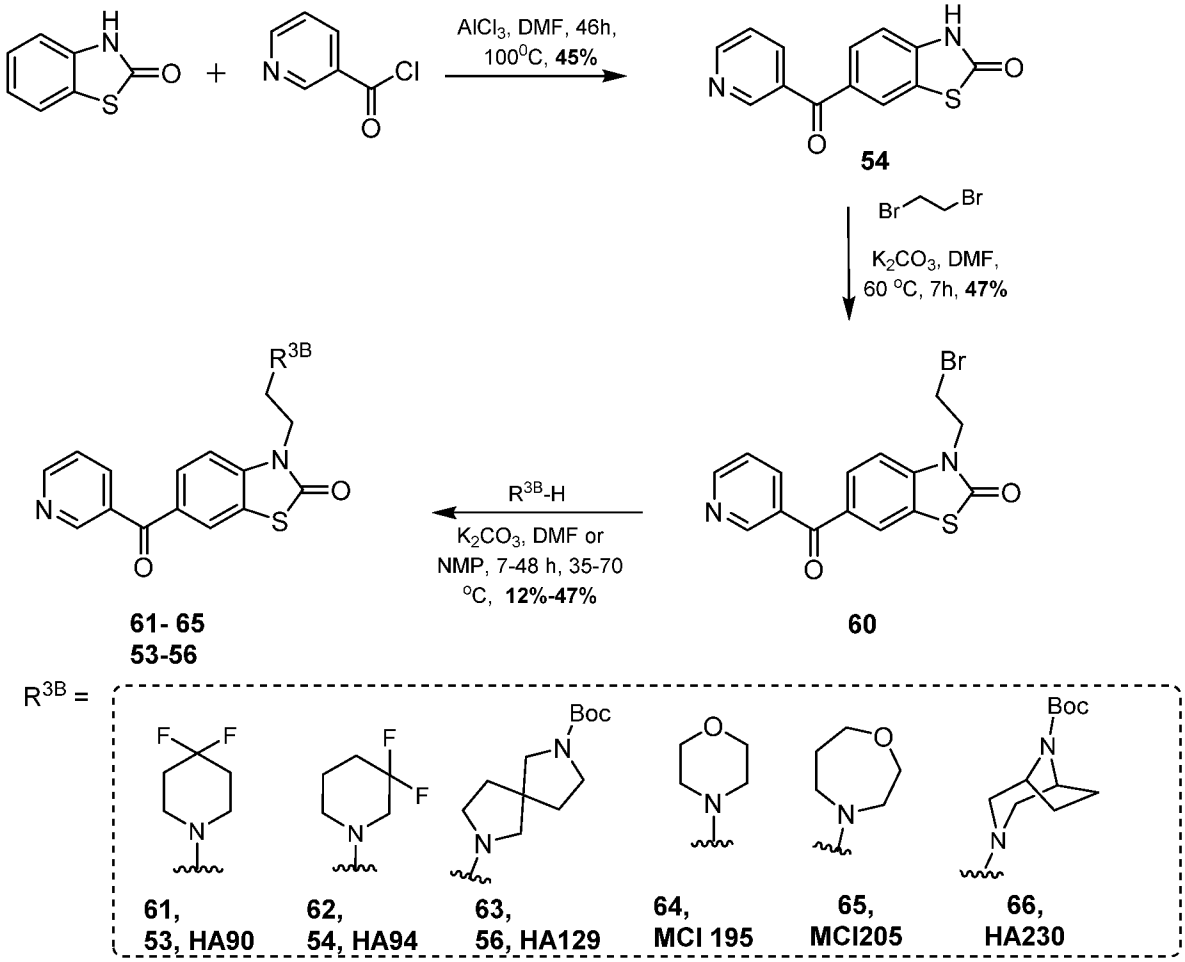
[0275] ***3-(2-(azepan-1-yl)ethyl)-6-(furan-2-carbonyl)benzo[d]thiazol-2(3H)-one hydrochloride, HA149 (58)***



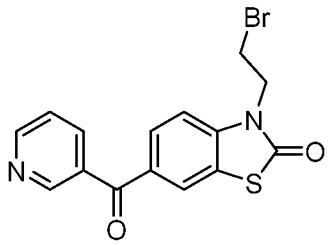
58, HA149

[0276] To a solution **53** (200 mg, 0.82 mmol, 1 equiv.) in THF (6 mL), 1-(2-chloroethyl) azepane hydrochloride (193.9 mg, 0.98 mmol, 1.2 equiv.), and potassium carbonate (338.12 mg, 2.45 mmol, 3 equiv.) were added. The reaction mixture was refluxed for 30 h. After being cooled, the mixture was filtered, and the filtrate was evaporated. The crude compound was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **58** (79 mg, 26%). To a solution of **58** (36 mg,0.097 mmol) in methanol (2 mL), excess 2N HCl in diethyl ether (0.6 mL) was added. The reaction mixture was stirred overnight at room temperature. Then, the solvents were removed by evaporation *in vacuo* and the residue was triturated with diethyl ether, then filtered to yield the hydrochloride salt as a white solid (37.8 mg, 96%). **^{1}H NMR** (600 MHz, Methanol-d_4) δ 8.28 (d, J = 1.8 Hz, 1H), 8.10 (dd, J = 8.5, 1.8 Hz, 1H), 7.92 (d, J = 1.6 Hz, 1H), 7.57 (d, J = 8.6 Hz, 1H), 7.40 (d, J = 3.7 Hz, 1H), 6.74 (dd, J = 3.6, 1.7 Hz, 1H), 4.53 (t, J = 6.6 Hz, 2H), 3.69 – 3.63 (m, 2H), 3.60 (t, J = 6.6 Hz, 2H), 3.38 – 3.32 (m, 2H), 2.07 – 1.88 (m, 4H), 1.83 – 1.72 (m, 4H). **^{13}C NMR** (JMOD, 151 MHz, MeOD) δ 182.00, 172.68, 153.44, 149.32, 141.18, 133.96, 129.91, 125.66, 124.31, 122.18, 113.70, 111.92, 56.54, 55.20, 39.04, 27.20, 24.87. **NB**: three carbons are overlapping. **UPLC/MS (Method B)**: t_R = 2.61 min, MS (ESI+) 371.32 $(M+H)^+$. **HRMS (ESI) for $C_{20}H_{23}N_2O_3S^+$**: Theoretical $[M+H]^+$= 371.1424 (4.3 ppm); found 371.1440.

[0277] Scheme 2B: Synthesis of Compounds of Formula (II)



[0278] ***3-(2-bromoethyl)-6-nicotinoylbenzo[d]thiazol-2(3H)-one, HA88 (60)***



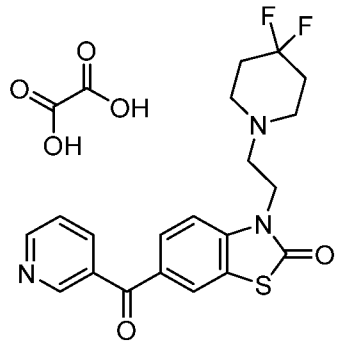
60, HA88

[0279] To a solution of **54** (2 g, 7.80 mmol, 1 equiv.) in DMF (10 mL), potassium carbonate (3.24 g, 23.41 mmol, 3 equiv.), and 1,2-dibromoethane (7.6 mL, 62.43 mmol, 8 equiv.) in DMF (2 mL) were added. The reaction mixture was heated at 60 °C for 7 h. After being cooled, the mixture was poured onto water and the aqueous layer was extracted with ethyl acetate. The

combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude compound was purified by silica gel chromatography using a gradient of hexane and ethyl acetate. The title compound was triturated with diethyl ether then filtered to afford **60** (1.34 g, 47.4%) as buff solid. **^{1}H NMR** (600 MHz, DMSO-d6) δ 8.89 (d, J = 2.2 Hz, 1H), 8.84 (dd, J = 4.9, 1.7 Hz, 1H), 8.22 (d, J = 1.8 Hz, 1H), 8.13 (dt, J = 7.8, 2.0 Hz, 1H), 7.81 (dd, J = 8.5, 1.8 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.61 (dd, J = 7.9, 4.8 Hz, 1H), 4.46 (t, J = 6.3 Hz, 2H), 3.83 (t, J = 6.3 Hz, 2H). **^{13}C NMR** (JMOD, 151 MHz, DMSO) δ 193.03, 169.75, 152.80, 149.97, 140.68, 137.16, 133.17, 131.48, 129.05, 125.43, 123.82, 122.08, 111.73, 43.84, 29.40. **UPLC/MS (Method A)**: t_R = 2.38 min, MS (ESI+) 363.27 $(M+H)^+$.

[0280] General procedure F: Synthesis of the 6-nicotinoylbenzothiazolone final compounds (61-65) with different *N*-heterocyclic amines. 3-(2-bromoethyl)-6-nicotinoylbenzo[d]thiazol-2(3H)-one 52 was dissolved in DMF or NMP, the corresponding *N*-heterocyclic amines and potassium carbonate were added. Using this procedure, the following compounds were obtained:

[0281] ***3-(2-(4,4-difluoropiperidin-1-yl)ethyl)-6-nicotinoylbenzo[d]thiazol-2(3H)-one oxalate, HA90 (61)***

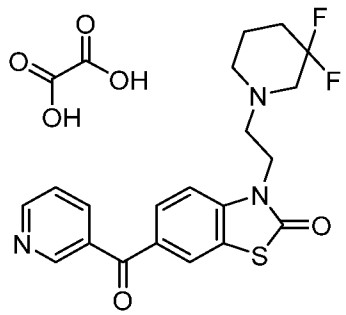


61, HA90

[0282] To a solution of **60** (150 mg, 0.41 mmol, 1 equiv.) in DMF (3 mL), 4,4-difluoropiperidine (64 µL, 0.62 mmol, 1.5 equiv.), and potassium carbonate (171.24 mg, 1.24 mmol, 3 equiv.) were added. The reaction was heated at 60 °C for 48 h. After cooling, the reaction mixture was poured onto water, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with brine, dried with Na_2SO_4, filtered, and the solvent was evaporated *in vacuo*. The crude compound was purified by basic alumina flash column chromatography using a gradient of hexane and ethyl acetate to afford **61** (33 mg, 20%). To a solution of the **61** (28.3 mg,

0.07 mmol, 1 equiv.) in diethyl ether, a solution of oxalic acid (6.3 mg, 0.07 mmol, 1 equiv.) in diethyl ether was added. The reaction mixture was left to stir overnight, then the salt was triturated with diethyl ether, and filtered to give the oxalate salt of **61** as a white solid (33.6 mg, 97%). **^{1}H NMR** (600 MHz, Methanol-d_4) δ 8.91 (s, 1H), 8.79 (dd, J = 5.0, 1.4 Hz, 1H), 8.23 (d, J = 7.8 Hz, 1H), 8.09 (d, J = 1.7 Hz, 1H), 7.88 (dd, J = 8.4, 1.6 Hz, 1H), 7.64 (dd, J = 7.8, 4.9 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 4.44 (t, J = 6.2 Hz, 2H), 3.40 (t, J = 6.3 Hz, 2H), 3.38 – 3.31 (m, 4H), 2.25 (tt, J = 12.2, 5.6 Hz, 4H). **^{13}C NMR** (JMOD, 151 MHz, MeOD) δ 184.82, 163.21, 154.34, 143.74, 141.37, 132.42, 129.70, 125.74, 123.90, 121.03, 116.74, 115.76, 111.51 (t, J = 241.5 Hz), 109.91, 102.59, 45.09, 41.73 (t, J = 5.4 Hz), 30.21, 23.49 (t, J = 25.3 Hz). **NB**: two carbons are overlapping. **UPLC/MS (Method A)**: t_R = 1.47 min, MS (ESI$^+$) 404.37 $(M+H)^+$. **HRMS (ESI) for $C_{20}H_{20}F_2N_3O_2S^+$**: Theoretical $[M+H]^+$= 404.1239 (4.7 ppm); found 404.1258.

[0283] ***3-(2-(3,3-difluoropiperidin-1-yl)ethyl)-6-nicotinoylbenzo[d]thiazol-2(3H)-one oxalate, HA94 (62)***

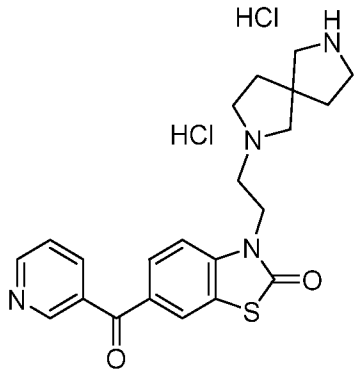


62, HA94

[0284] To a solution of **60** (200 mg, 0.55 mmol, 1 equiv.) in DMF (3 mL), 3,3-difluoropiperidine hydrochloride (130.14 mg, 0.83 mmol, 1.5 equiv.), and potassium carbonate (228.3 mg, 1.65 mmol, 3 equiv.) were added. The reaction was heated at 60 °C for 24 h. After cooling, the reaction mixture was poured onto water, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with brine, dried with Na_2SO_4, filtered, and the solvent was evaporated *in vacuo*. The crude compound was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **62** (54 mg, 24.3%). To a solution of the **62** (25 mg, 0.06 mmol, 1 equiv.) in diethyl ether, a solution of oxalic acid (5.6 mg, 0.06 mmol, 1 equiv.) in diethyl ether was added. The reaction mixture was left to stir overnight, then the salt was triturated with diethyl ether, and filtered to give the oxalate salt of **62**

as a white solid (29.4 mg, 95.4%). **^{1}H NMR** (600 MHz, Methanol-d_4) δ 8.90 (d, J = 2.2 Hz, 1H), 8.80 (dd, J = 5.0, 1.6 Hz, 1H), 8.23 (dt, J = 7.9, 1.8 Hz, 1H), 8.10 – 8.08 (m, 1H), 7.87 (dt, J = 8.5, 1.8 Hz, 1H), 7.65 (dd, J = 7.8, 5.0 Hz, 1H), 7.49 (d, J = 8.5 Hz, 1H), 4.34 – 4.29 (m, 2H), 3.18 – 3.07 (m, 4H), 2.92 – 2.84 (m, 2H), 2.02 – 1.93 (m, 2H), 1.86 – 1.80 (m, 2H). **^{13}C NMR** (JMOD, 151 MHz, MeOD) δ 194.27, 172.27, 163.12, 153.09, 150.74, 142.34, 139.23, 135.30, 133.10, 130.42, 126.07, 125.26, 124.42, 120.84 (t, J = 241.5 Hz), 112.20, 58.38 (t, J = 30.0 Hz), 55.33, 53.28, 40.60, 32.45 (t, J = 23.2 Hz), 22.11 (t, J = 4.2 Hz). **UPLC/MS (Method A)**: t_R = 1.99 min, MS (ESI$^+$) 404.40 $(M+H)^+$. **HRMS (ESI) for $C_{20}H_{20}F_2N_3O_2S^+$**: Theoretical [M+H]+= 404.1239 (3.7 ppm); found 404.1254.

[0285] ***3-(2-(2,7-diazaspiro[4.4]nonan-2-yl)ethyl)-6-nicotinoylbenzo[d]thiazol-2(3H)-one dihydrochloride, HA129 (63)***

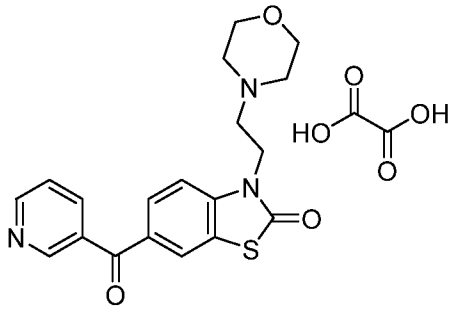


63, HA129

[0286] To a solution of **60** (200 mg, 0.55 mmol, 1 equiv.) in NMP (3 mL), tert-butyl 2,7-diazaspiro[4.4]nonane-2-carboxylate (186.92 mg, 0.83 mmol, 1.5 equiv.) and potassium carbonate (228.3 mg, 1.65 mmol, 3 equiv.) were added. The reaction was stirred at room temperature for 2 h, no product was detected by LCMS, then the reaction mixture was heated at 70 °C for 4 h. After cooling, the reaction mixture was poured onto water, and the aqueous layer was extracted with DCM. The combined organic extract was washed with brine, dried with Na_2SO_4, filtered, and the solvent was evaporated *in vacuo*. The crude compound was purified by silica gel chromatography using a gradient of DCM and methanol to afford **63** (65 mg, 23.2%). To a solution of **63** (25 mg, 0.049 mmol) in methanol, excess 4N HCl in dioxane (0.3 mL) was added. The reaction mixture was stirred at room temperature overnight, the boc deprotection was confirmed by LCMS. The solvent was evaporated *in vacuo* and the residue was triturated with

diethyl ether to afford **63** (21.5 mg, 92.6%) as a buff solid of the dihydrochloride salt. **^{1}H NMR Free base** (600 MHz, Methanol-d_4) (mixture of diastereomers are overlapping), δ 8.91 (s, 2H), 8.80 (d, J = 5.0 Hz, 2H), 8.21 (d, J = 7.8 Hz, 2H), 8.13 – 8.04 (m, 2H), 7.87 (d, J = 7.2 Hz, 2H), 7.69 – 7.59 (m, 2H), 7.47 (d, J = 7.6 Hz, 2H), 4.32 – 4.16 (m, 4H), 3.49 – 3.36 (m, 4H), 3.31 – 3.14 (m, 4H), 3.01 – 2.59 (m, 10H), 2.42 – 2.31 (m, 2H), 2.12 – 1.75 (m, 8H), 1.46 (s, 18H). **^{13}C NMR free base** (JMOD, 151 MHz, MeOD) δ 194.33, 171.99 (2C), 156.47 (2C), 153.28, 150.93, 142.50, 138.97, 135.21, 132.99, 130.48 (2C), 126.06, 125.16, 124.40, 112.12, 80.87 (2C), 64.66, 58.49, 57.81, 55.12 (2C), 53.88 (2C), 50.82, 49.36, 48.64, 46.50, 46.07, 42.55, 38.34, 37.52, 36.01, 35.89, 31.68, 28.78. **NB**: Spectrum represents a mixture of two diastereomers; thirteen additional carbon signals exist; i.e. sixteen carbon signals are missing due to overlap from the two isomers). **UPLC/MS (Method B) free base**: t_R = 2.65 min, MS (ESI$^+$) 509.48 $(M+H)^+$. **UPLC/MS (Method C) salt**: t_R = 3.16 min, MS (ESI$^+$) 409.36 $(M+H)^+$.

[0287] ***3-[2-(Morpholin-4-yl)ethyl]-6-(pyridine-3-carbonyl)-2,3-dihydro-1,3-benzothiazol-2-one oxalate, MCI195 (64)***

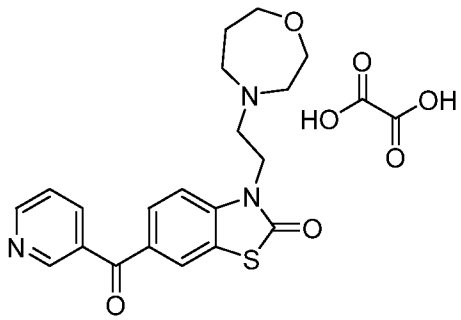


64, MCI195

[0288] To a solution of **60** (150 mg, 0.58 mmol, 1 equiv.) in DMF (2 mL), 4-(2-chloroethyl)morpholine hydrochloride (131 mg, 0.704 mmol, 1.2 equiv.), potassium carbonate (210 mg, 1.24 mmol, 3 equiv.), potassium iodide (catalytic amount) were added. The reaction mixture was heated at 60 °C for 4 h. After cooling, the mixture was poured onto water, and the aqueous layer was extracted with DCM. The combined organic extract was washed with brine, dried with Na_2SO_4, filtered, and the solvent was evaporated *in vacuo*. The crude compound was purified by silica gel chromatography using a mixture of ethyl acetate and methanol (9:1, v/v) as an eluent to afford the free base of **64** (184 mg, 85%) as a yellow solid. The free base was then converted into the oxalate salt for biological test to give **64** as a white solid.**^{1}H NMR** (600 MHz,

Methanol-d_4) δ 8.89 (d, J = 2.2 Hz, 1H), 8.78 (dd, J = 4.9, 1.6 Hz, 1H), 8.21 (dt, J = 7.9, 1.9 Hz, 1H), 8.06 (d, J = 1.7 Hz, 1H), 7.86 (dd, J = 8.5, 1.8 Hz, 1H), 7.62 (dd, J = 7.9, 4.9 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 4.46 (t, J = 6.4 Hz, 2H), 3.89 (t, J = 4.7 Hz, 4H), 3.47 (t, J = 6.4 Hz, 2H), 3.35 (d, J = 1.4 Hz, 4H). **^{13}C NMR** (151 MHz, Methanol-d_4) δ 194.1, 172.7, 163.9 (2C), 152.9, 150.6, 141.6, 139.6, 135.3, 133.4, 130.6, 126.2, 125.4, 124.5, 112.1, 65.0 (2C), 55.1, 53.6, 38.1. **UPLC/MS (Method A)**: t_R = 0.61 min, MS (ESI+) 370.50 $(M+H)^+$.

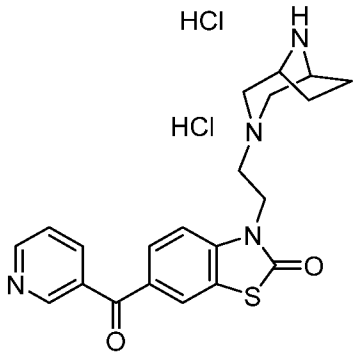
[0289] ***3-[2-(1,4-Oxazepan-4-yl)ethyl]-6-(pyridine-3-carbonyl)-2,3-dihydro-1,3-benzothiazol-2-one oxalate, MCI205 (65)***



65, MCI205

[0290] To a solution of **60** (202 mg, 0.56 mmol, 1 equiv.) in DMF (3 mL), 1,4-oxazepane (84 mg, 0.83 mmol, 1.5 equiv.), potassium carbonate (230 mg, 1.67 mmol, 3 equiv.), potassium iodide (catalytic amount) were added. The reaction mixture was heated at 60 °C overnight. After cooling, the mixture was poured onto water, and the aqueous layer was extracted with DCM. The combined organic extract was washed with brine, dried with Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The crude compound was purified by silica gel chromatography using an initial gradient of ethyl acetate and methanol, and then isocratic (9:1, v/v) to afford the free base of **65** (41 mg, 20%) as a yellow oil. The free base was then converted into the oxalate salt for biological test to give **65** as a white solid. **^{1}H NMR** (600 MHz, Methanol-d_4) δ 8.88 (d, J = 2.0 Hz, 1H), 8.78 (dd, J = 5.0, 1.5 Hz, 1H), 8.20 (dt, J = 7.9, 1.9 Hz, 1H), 8.04 (d, J = 1.6 Hz, 1H), 7.88 – 7.83 (m, 1H), 7.62 (dd, J = 7.9, 4.9 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 4.50 (t, J = 6.5 Hz, 2H), 3.96 – 3.91 (m, 2H), 3.83 (t, J = 5.9 Hz, 2H), 3.65 – 3.54 (m, 6H), 2.20 (p, J = 5.7 Hz, 2H). **^{13}C NMR** (151 MHz, Methanol-d_4) δ 194.3, 172.5, 166.1 (2C), 153.3, 150.9, 141.7, 139.1, 135.1, 133.4, 130.6, 126.2, 125.2, 124.4, 112.1, 68.9, 64.7, 58.2, 55.0, 54.7, 39.1, 27.1. **UPLC/MS (Method A)**: t_R = 0.75 min, MS (ESI+) 384.39 $(M+H)^+$.

[0291] ***3-(2-(3,8-diazabicyclo[3.2.1]octan-3-yl)ethyl)-6-nicotinoylbenzo[d]thiazol-2(3H)-one dihydrochloride, HA230 (66)***



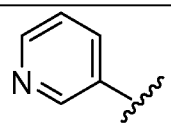
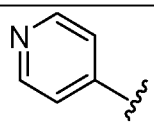
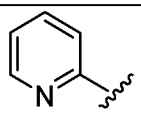
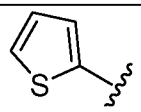
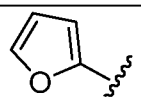
66, HA230

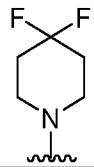
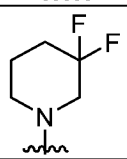
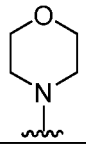
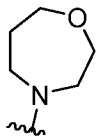
[0292] To a solution of **60** (200 mg, 0.55 mmol, 1 equiv.) in NMP (3 mL), tert-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (175.31 mg, 0.83 mmol, 1.5 equiv.), and potassium carbonate (228.25 mg, 1.65 mmol, 3 equiv.) were added. The reaction was heated at 35 °C for 48 h. After cooling, the reaction mixture was poured onto water, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with brine, dried with Na_2SO_4, filtered, and the solvent was evaporated *in vacuo*. The crude compound was purified by silica gel chromatography using a gradient of DCM and methanol to afford **66** (130 mg, 47.7%). To a solution of **66** (85 mg, 0.17 mmol) in DCM, excess 4N HCl in dioxane (1 mL) was added. The reaction mixture was stirred at room temperature for 18 h, the boc deprotection was monitored by LCMS. The solvent was evaporated *in vacuo* and the residue was triturated with diethyl ether to afford **66** as a white solid of the dihydrochloride salt (65 mg, 95.9%). **^{1}H NMR** (600 MHz, Deuterium Oxide) δ 9.16 (dd, *J* = 1.8, 0.8 Hz, 1H), 9.04 – 8.99 (m, 1H), 8.82 (dt, *J* = 8.0, 1.8 Hz, 1H), 8.17 (m, 2H), 7.97 (ddd, *J* = 8.6, 1.9, 0.7 Hz, 1H), 7.55 (d, *J* = 8.6 Hz, 1H), 4.33 (t, *J* = 6.0 Hz, 2H), 4.13 – 4.08 (m, 2H), 3.20 – 3.16 (m, 2H), 3.07 (t, *J* = 6.0 Hz, 2H), 2.83 (d, *J* = 12.7 Hz, 2H), 2.06 – 1.92 (m, 4H). **^{13}C NMR** (JMOD, 151 MHz, MeOD) δ 190.41, 172.30, 147.42, 145.69, 144.51, 142.86, 138.21, 131.77, 130.70, 128.57, 126.50, 124.65, 112.54, 56.58, 56.30, 54.80, 40.52, 26.32. **NB**: three carbons are overlapping. **UPLC/MS (Method B)**: t_R = 2.23 min, MS (ESI$^+$) 395.35 $(M+H)^{+\cdot}$ **HRMS (ESI) for $C_{21}H_{22}N_4O2S^+$**: Theoretical $[M+H]^+$= 395.1536 (4.3 ppm); found 395.1553.

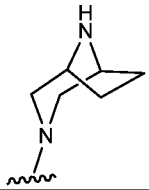
Metabolic Stability

[0293] Metabolic stability studies on compounds of Formula (II) were carried out as described above.

[0294] Table 2A: *In vitro* metabolic stability

Comp.	Compound code	R^{3A}	$t_{½}$ (min)	Cl_{int} (µl/min/mg)
59	**MCI194**		2.8	246.3
55	**HA151**		**11.3**	61.5
56	**HA144**		1.9	372.7
57	**HA216**		0.9	749
58	**HA149**		1.0	682.3

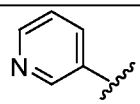
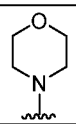
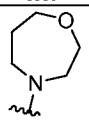
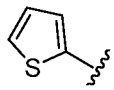
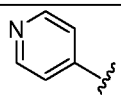
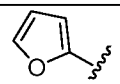
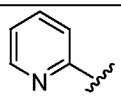
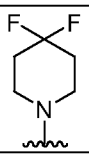
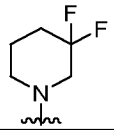
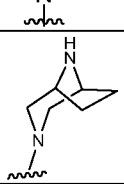
Comp.	Compound code	R^{3B}	$t_{½}$ (min)	Cl_{int} (µl/min/mg)
61	**HA90**		1.6	443.0
62	**HA94**		1.0	715.5
64	**MCI 195**		4.7	148.5
65	**MCI 205**		3.9	177.1

66	**HA230**		**>30**	13.4

Binding Affinity

[0295] Binding affinity studies on compounds of Formula (II) were carried out as described above.

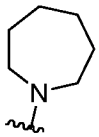
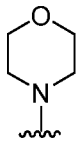
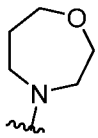
[0296] Table 2B: *In vitro* binding affinity

#	Comp code	R^{3B}	K_i (nM ± SD)	
			σ_1R	σ_2R
59	MCI194		**ND**	155.36 ± 32.99
64	MCI195		**ND**	**ND**
65	MCI205		**ND**	**ND**
57	HA216		**32.42** ± 22.34	**335.60** ± 37.96
55	HA151		27.45 ± 9.56	**372.05** ± 7.46
58	HA149		36.12 ± 6.31	**290.84** ± 100.61
56	HA144		**226.78** ± 44.46	**ND**
61	HA90		ND	ND
62	HA94		ND	ND
60	HA230		ND	ND

Permeability

[0297] Permeability studies on compounds of Formula (II) were carried out as described above.

[0298] Table 2C: In vitro permeability

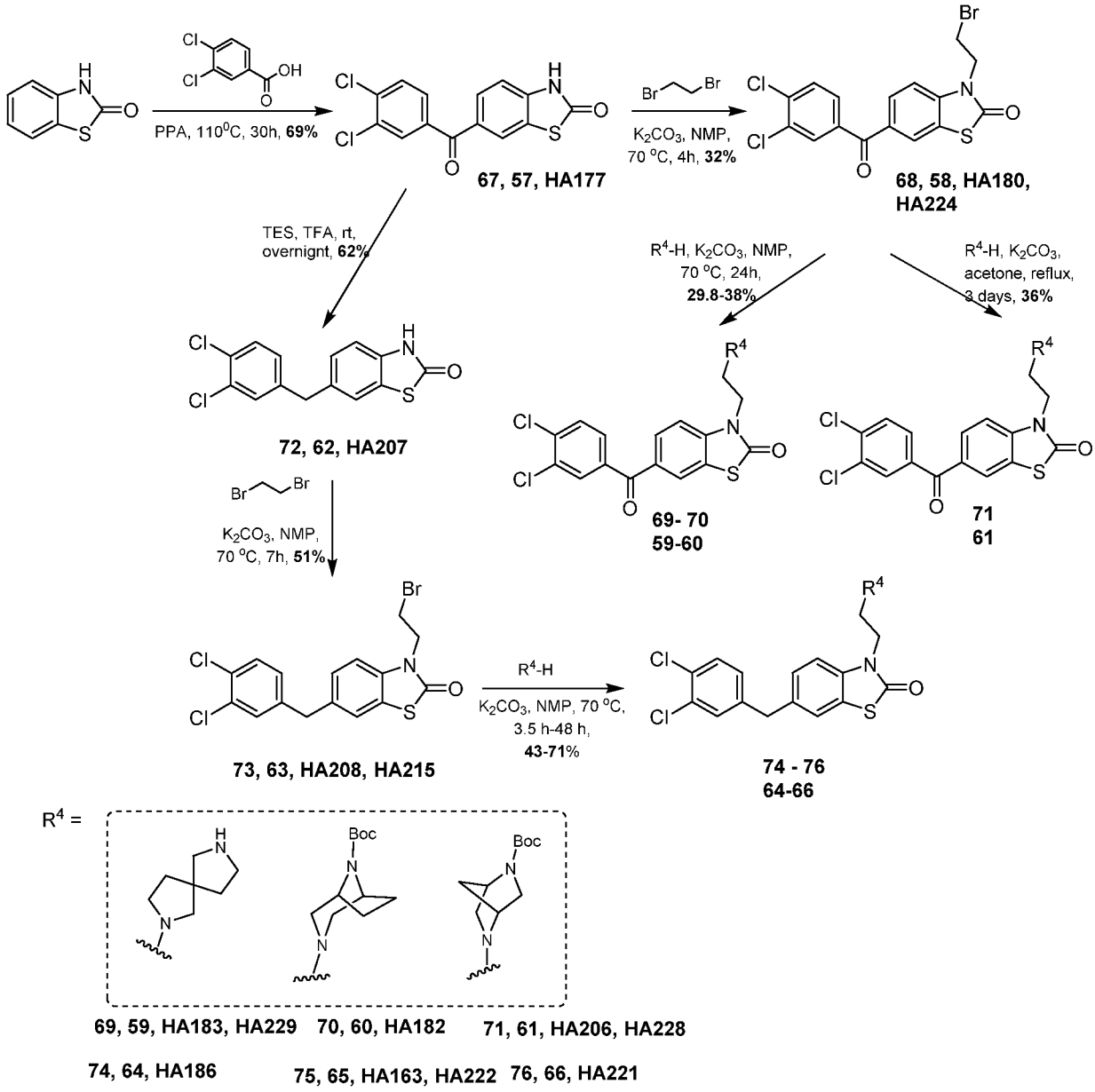
Comp numb	Comp code	R^{3B}	Caco-2 Permeability (P_{app}, 10^{-6} cm/sec)	Permeability Class	tPSA
CM304	-	-	19.09 ± 1.73	High	23.55
-	**MCI 194**		25.09±2.16	High	52.98
64	**MCI 195**		23.38±0.22	High	62.21
65	**MCI 205**		22.89±0.52	High	62.21

Compounds of Formula (III)

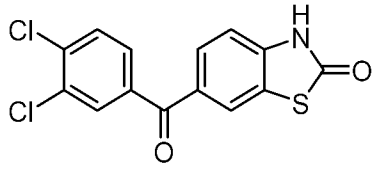
Synthesis

[0299] The below scheme exemplifies the synthetic route utilized to prepare compounds of Formula (III).

[0300] Scheme 3: Synthesis of Compounds of Formula (III)



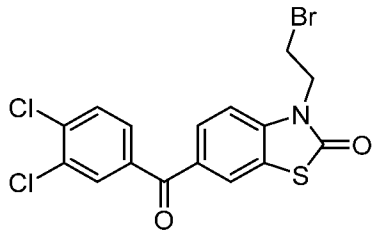
[0301] ***6-(3,4-Dichlorobenzoyl)-2,3-dihydro-1,3-benzothiazol-2-one, HA177 (67)***



67, HA177

[0302] The organic acid 3,4-dichlorobenzoic acid (2779 mg, 13.23 mmol, 1.1 equiv.) was slowly added to a solution of benzothiazolone (2000 mg, 14.54 mmol, 1 equiv.) in PPA (40 g). The mixture was stirred and heated at 110°C. After 30 h, the mixture was cooled and poured onto ice/H_2O and was stirred overnight. The resulting precipitate was collected by filtration, washed with water and methanol. Then, the title compound was isolated after the neutralization with 1 M NaOH solution and extraction with ethyl acetate to afford **67** (2956 mg, 69%). **^{1}H NMR** (600 MHz, Methanol-d_4) δ 7.88 (d, J = 1.9 Hz, 1H), 7.86 (d, J = 1.9 Hz, 1H), 7.69 (d, J = 8.3 Hz, 1H), 7.63 (dd, J = 8.3, 2.0 Hz, 1H), 7.61 (dd, J = 8.4, 1.9 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H). **^{13}C NMR** (151 MHz, MeOD) δ 194.8, 173.7, 140.1, 136.9, 133.6, 132.3, 131.6, 131.5, 130.2, 129.6, 129.5, 124.7, 124.6, 114.9. **UPLC/MS (Method B)**: t_R = 3.67 min, MS (ESI$^+$) 324.41 $(M+H)^+$

[0303] ***3-(2-Bromoethyl)-6-(3,4-dichlorobenzoyl)-2,3-dihydro-1,3-benzothiazol-2-one, HA180 (68)***



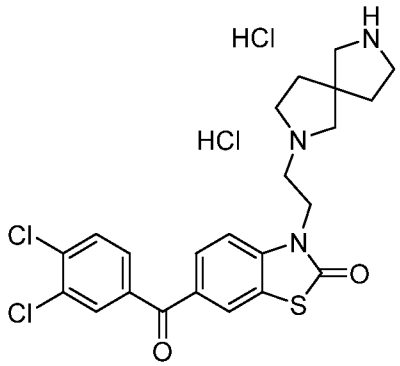
68, HA180, HA224

[0304] To a solution of **67** (1700 mg, 5.24 mmol, 1 equiv.) in NMP (6 mL), potassium carbonate (2174 mg, 15.73 mmol, 3 equiv.), and 1,2-dibromoethane (3.6 mL, 41.95 mmol, 8 equiv.) in NMP (2 mL) were added. The reaction mixture was heated at 70 °C for 4 h. After being cooled, the mixture was poured onto water and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude compound was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **68** (723 mg, 32%). **^{1}H NMR** (600 MHz, Chloroform-d) δ 7.91

(d, J = 1.8 Hz, 1H), 7.84 (d, J = 1.8 Hz, 1H), 7.77 (dd, J = 8.4, 1.8 Hz, 1H), 7.60 – 7.54 (m, 2H), 7.23 (d, J = 8.5 Hz, 1H), 4.39 (t, J = 6.8 Hz, 2H), 3.66 (t, J = 6.8 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 192.3, 169.9, 140.4, 137.1, 133.1, 131.9, 131.6, 130.6, 129.1, 128.8, 124.9, 123.2, 110.3, 44.5, 27.0.

[0305] General method A for the synthesis of compounds (69-70): To a solution of **68** (200 mg, 0.46 mmol, 1 equiv.) in NMP (2 mL), the corresponding amine (1.5 equiv.) in NMP (1 mL) and potassium carbonate (192.34 mg, 1.39 mmol, 3 equiv.) were added. The reaction was heated at 70 °C overnight. After cooling, the reaction mixture was poured onto water, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with brine, dried with Na_2SO_4, filtered, and the solvent was evaporated *in vacuo*. The crude compound was purified by silica gel chromatography using a gradient of hexane and ethyl acetate.

[0306] ***3-(2-{2,7-Diazaspiro[4.4]nonan-2-yl}ethyl)-6-(3,4-dichlorobenzoyl)-2,3-dihydro-1,3-benzothiazol-2-one dihydrochloride, HA183 (69)***



69, HA183

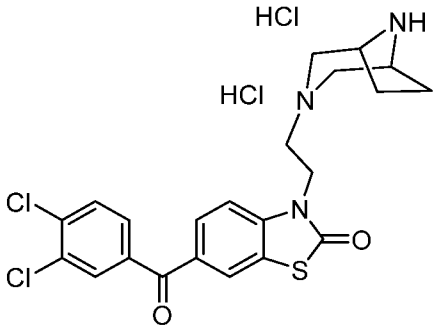
[0307] The corresponding amine: tert-butyl 2,7-diazaspiro[4.4]nonane-2-carboxylate (157.48 mg, 0.69 mmol, 1.5 equiv.). Yield (85 mg, 38.4%).

[0308] To a solution of **69** (85 mg, 0.17 mmol) in DCM, excess 4N HCl in dioxane (0.5 mL) was added. The reaction mixture was stirred at room temperature, and the boc deprotection was monitored by LCMS. After 48 h, the solvent was evaporated *in vacuo* and the salt residue was repurified by silica gel chromatography using a gradient of DCM and methanol to afford **69** as a dihydrochloride salt (55.6 mg, combined yield 21.8%).

[0309] Other method. To a solution of **68** (200 mg, 0.46 mmol, 1 equiv.) in acetone (20 mL), the corresponding amine ((157.48 mg, 0.69 mmol,1.5 equiv.) in acetone (1 mL) and potassium

carbonate (192.34 mg, 1.39 mmol, 3 equiv.) were added. The reaction was refluxed for 4 days and the completion of the reaction was monitored by LCMS. The solvents were evaporated *in vacuo*. The crude compound was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **69** in lower yield (27.6%). **^{1}H NMR** (600 MHz, Methanol-d_4) δ 8.08 (d, J = 1.7 Hz, 1H), 7.91 (d, J = 1.9 Hz, 1H), 7.86 (dd, J = 8.5, 1.8 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.68 (dd, J = 8.3, 2.0 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 4.57 – 4.30 (m, 2H), 3.70 – 3.31 (m, 10H), 2.25 – 2.05 (m, 4H). **^{13}C NMR** (151 MHz, MeOD) δ 193.9, 172.4, 141.9, 138.9, 137.7, 133.8, 133.1, 132.5, 131.8, 130.48, 130.43, 126.0, 124.4, 112.0, 63.1, 55.4, 54.8, 53.4, 49.4, 46.0, 41.3, 36.9, 35.5. **N.B:** Before chromatographic purification of the salt, the salt of **69** demonstrated complexity in the NMR spectra most likely arising from diastereomeric mixtures of the salt. **UPLC/MS (Method B)**: t_R = 2.60 min, MS (ESI$^+$) 476.27 $(M+H)^+$. **HRMS (ESI) for $C_{23}H_{24}Cl_2N_3O_2S^+$**: Theoretical $[M+H]^+$= 476.0961 (2.5 ppm); found 476.0973.

[0310] ***3-(2-{3,8-Diazabicyclo[3.2.1]octan-3-yl}ethyl)-6-(3,4-dichlorobenzoyl)-2,3-dihydro-1,3-benzothiazol-2-one dihydrochloride, HA182 (70)***

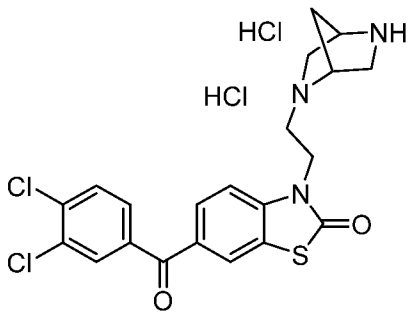


70, HA182

[0311] The corresponding amine: tert-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (147.7 mg, 0.69 mmol, 1.5 equiv.). Yield (77.7 mg, 29.8%). To a solution of **70** (77.7 mg, 0.17 mmol) in methanol, excess 4N HCl in dioxane (0.8 mL) was added. The reaction mixture was stirred at room temperature for 12 h, the boc deprotection was monitored by LCMS. The solvent was evaporated *in vacuo* and the residue was triturated with diethyl ether to afford **70** as the dihydrochloride salt (82.4 mg, combined yield 33.1%). **^{1}H NMR** (600 MHz, Methanol-d_4) δ 8.08 – 8.04 (m, 1H), 7.91 – 7.87 (m, 1H), 7.85 – 7.82 (m, 1H), 7.71 (dd, J = 8.3, 2.5 Hz, 1H), 7.69 – 7.65 (m, 1H), 7.61 (d, J = 8.4 Hz, 1H), 4.49 – 4.38 (m, 2H), 4.30 – 4.18 (m, 2H), 3.71 – 3.48 (m, 2H), 3.31 – 3.20 (m, 4H), 2.36 – 2.10 (m, 4H). **^{13}C NMR** (151 MHz, MeOD) δ 193.9, 172.7,

141.7, 138.9, 137.7, 133.8, 133.3, 132.5, 131.8, 130.5, 130.4, 126.1, 124.4, 112.1, 55.9 (2C), 55.6 (2C), 55.3, 39.3, 25.7 (2C). **UPLC/MS (Method B)**: t_R = 2.96 min, MS (ESI$^+$) 462.22 (M+H)$^+$. **HRMS (ESI) for $C_{22}H_{22}Cl_2N_3O_2S^+$:** Theoretical [M+H]$^+$= 462.0804 (2.8 ppm); found 462.0817.

[0312] ***3-(2-{2,5-Diazabicyclo[2.2.1]heptan-2-yl}ethyl)-6-(3,4-dichlorobenzoyl)-2,3-dihydro-1,3-benzothiazol-2-one dihydrochloride, HA228 (71)***



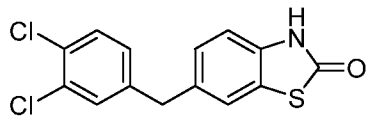
71, HA228

[0313] To a solution of **68** (200 mg, 0.46 mmol, 1 equiv.) in NMP (2 mL), (1S,4S)-(−)-2-Boc-2,5-diazabicyclo[2.2.1]heptane (70 mg, 0.35 mmol, 1 equiv.) in NMP (1 mL) and potassium carbonate (192.34 mg, 1.39 mmol, 3 equiv.) were added. The reaction was heated at 50 °C for 48h. After cooling, the reaction mixture was poured onto water, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with brine, dried with Na_2SO_4, filtered, and the solvent was evaporated *in vacuo*. The crude compound was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **71** in a low yield of <10%.

[0314] **Alternative method**. To a solution of **68** (200 mg, 0.46 mmol, 1 equiv.) in acetone (20 mL), (1S,4S)-(−)-2-Boc-2,5-diazabicyclo[2.2.1]heptane (70 mg, 0.35 mmol, 1 equiv.) in acetone (1 mL) and potassium carbonate (192.34 mg, 1.39 mmol, 3 equiv.) were added. The reaction was refluxed for 3 days and the completion of the reaction was monitored by LCMS. The solvents were evaporated *in vacuo*. The crude compound was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **71** in a higher yield (71 mg, 36.7%). To a solution of **71** (71 mg, 0.13 mmol) in methanol, excess 4N HCl in dioxane (0.5 mL) was added. The reaction mixture was stirred at room temperature, and the boc deprotection was monitored by LCMS. After 42 h, the solvent was evaporated *in vacuo* to afford the salt of **71** (63 mg,

combined yield 34.2%). The salt was purified by silica gel chromatography using a gradient of DCM and methanol to afford **71** as a dihydrochloride salt (43 mg). **^{1}H NMR** (600 MHz, Methanol-d_4) δ 8.03 (d, J = 1.6 Hz, 1H), 7.89 (d, J = 1.9 Hz, 1H), 7.83 (dd, J = 8.4, 1.8 Hz, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.67 (dd, J = 8.3, 2.0 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 4.29 – 4.09 (m, 3H), 3.81 – 3.71 (m, 1H), 3.34 – 3.33 (m, 1H), 3.16 (d, J = 11.2 Hz, 1H), 3.11 – 2.90 (m, 4H), 2.07 (d, J = 11.3 Hz, 1H), 1.82 (d, J = 11.2 Hz, 1H). **^{13}C NMR** (151 MHz, MeOD) δ 194.0, 172.1, 142.3, 139.0, 137.7, 133.8, 132.9, 132.5, 131.8, 130.4 (2C), 125.9, 124.2, 112.1, 61.3, 59.7, 56.9, 52.6, 50.7, 42.9, 34.6. **UPLC/MS (Method B)**: t_R = 2.94 min, MS (ESI$^+$) 448.20 (M+H)$^+$. **HRMS (ESI) for $C_{21}H_{19}Cl_2N_3O_2S^+$**: Theoretical [M+H]$^+$= 448.0648 (2.5 ppm); found 448.0659.

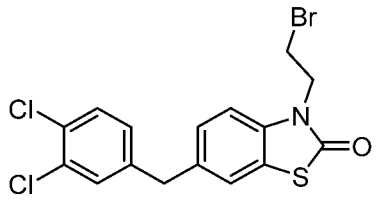
[0315] ***6-[(3,4-Dichlorophenyl)methyl]-2,3-dihydro-1,3-benzothiazol-2-one, HA207 (72)***



72, HA207

[0316] Triethylsilane (2.8 mL, 17.4 mmol, 10 equiv.) was added dropwise to a stirred solution of **67** (566 mg, 1.74 mmol, 1 equiv.) in trifluoracetic acid (25 mL). The mixture was stirred at room temperature for overnight and then poured onto ice. The resulting precipitate was stirred for 1 h, filtered, washed with cold water, ethanol and petroleum ether, then dried to afford **72** (338 mg, 62.4%). The crude was used for the next step without further purification. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.53 (d, J = 8.2 Hz, 1H), 7.52 (d, J = 2.1 Hz, 1H), 7.45 (d, J = 1.7 Hz, 1H), 7.22 (dd, J = 8.3, 2.1 Hz, 1H), 7.14 (dd, J = 8.1, 1.8 Hz, 1H), 7.03 (d, J = 8.1 Hz, 1H), 3.93 (s, 2H). **^{13}C NMR** (151 MHz, DMSO) δ 170.0, 142.7, 135.2, 134.6, 130.9, 130.58, 130.54, 129.0, 128.6, 126.9, 123.8, 122.6, 111.6, 39.9. **UPLC/MS (Method B)**: t_R = 3.57 min, MS (ESI$^+$) 310.23 (M+H)$^+$ and 312.19 (M+3H)$^+$.

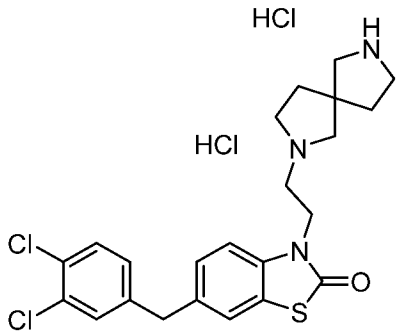
[0317] ***3-(2-Bromoethyl)-6-[(3,4-dichlorophenyl)methyl]-2,3-dihydro-1,3-benzothiazol-2-one, HA215 (73)***



73, HA215

[0318] To a solution of **72** (325 mg, 1.05 mmol, 1 equiv.) in NMP (3 mL), potassium carbonate (434 mg, 3.14 mmol, 3 equiv.), and 1,2-dibromoethane (0.72 mg, 8.38 mmol, 8 equiv.) in NMP (2 mL) were added. The reaction mixture was heated at 70 °C for 7 h. After being cooled, the mixture was poured onto water and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude compound was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **73** (222.8 mg, 51%). **TLC/MS:** MS (ESI^+) 416.20 $(M+H)^+$

[0319] ***3-(2-{2,7-Diazaspiro[4.4]nonan-2-yl}ethyl)-6-[(3,4-dichlorophenyl)methyl]-2,3-dihydro-1,3-benzothiazol-2-one dihydrochloride, HA186 (74)***

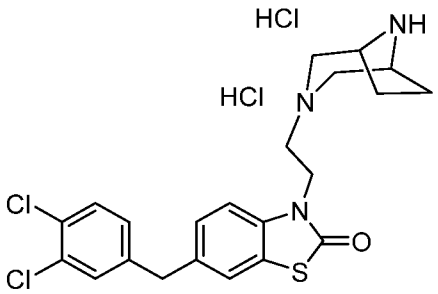


74, HA186

[0320] To a solution of **73** (185 mg, 0.44 mmol, 1 equiv.) in NMP (3 mL), tert-butyl 2,7-diazaspiro[4.4]nonane-2-carboxylate (150 mg, 0.66 mmol, 1.5 equiv.), and potassium carbonate (183.9 mg, 1.3 mmol, 3 equiv.) were added. The reaction was heated at 70 °C for 16 h. After cooling, the reaction mixture was poured onto water, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with brine, dried with Na_2SO_4, filtered, and the solvent was evaporated *in vacuo*. The crude compound was purified by silica gel

chromatography using a gradient of hexane and ethyl acetate to afford **74** (147 mg, 71.8%). To a solution of **74** (147 mg, 0.31 mmol) in methanol, excess 4N HCl in dioxane (0.8 mL) was added. The reaction mixture was stirred at room temperature overnight, the boc deprotection was monitored by LCMS. The solvent was evaporated *in vacuo* and the residue was triturated with diethyl ether to afford **74** as the dihydrochloride salt (164 mg, combined yield 64%). **^{1}H NMR** (600 MHz, Methanol-d_4) (mixture of diastereomers are overlapping), δ 7.45 (d, J = 1.6 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 2.0 Hz, 2H), 7.28 (dd, J = 8.3, 1.6 Hz, 2H), 7.16 (dd, J = 8.3, 2.1 Hz, 2H), 4.45 – 4.40 (m, 4H), 4.05 – 3.88 (m, 8H), 3.75 – 3.60 (m, 4H), 3.50 – 3.36 (m, 12H), 2.39 – 2.12 (m, 8H). **^{13}C NMR** (151 MHz, MeOD) δ 172.7, 143.4, 137.9, 136.0, 133.2, 131.7, 131.5, 131.0, 129.7, 128.8, 124.3, 124.2, 112.3, 62.4 (2C), 55.3 (2C), 53.8 (2C), 49.2, 46.0 (2C), 41.1, 39.8, 36.9 (2C), 35.3 (2C). **N.B**: Spectrum represents a mixture of two diastereomers (five additional carbon signals exist from the second isomer; i.e. eighteen carbon signals are missing due to overlap from the two isomers). **UPLC/MS (Method B)**: t_R = 2.52 min, MS (ESI$^+$) 462.24 (M+H)$^+$. **HRMS (ESI) for $C_{23}H_{26}Cl_2N_3OS^+$**: Theoretical [M+H]$^+$= 462.1168 (2.6 ppm); found 462.1180.

[0321] ***3-(2-{3,8-Diazabicyclo[3.2.1]octan-3-yl}ethyl)-6-[(3,4-dichlorophenyl)methyl]-2,3-dihydro-1,3-benzothiazol-2-on dihydrochloride, HA163, HA222 (75)***

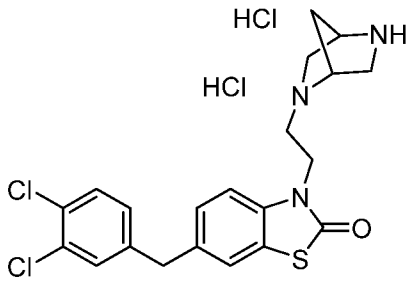


75, HA163

[0322] To a solution of **73** (200 mg, 0.47 mmol, 1 equiv.) in NMP (3 mL), tert-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (152.67 mg, 0.72 mmol, 1.37 equiv.), and potassium carbonate (198.79 mg, 1.43 mmol, 3 equiv.) were added. The reaction was heated at 70 °C 48 h. After cooling, the reaction mixture was poured onto water, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with brine, dried with Na_2SO_4, filtered, and the solvent was evaporated *in vacuo*. The crude compound was purified by silica gel

chromatography using a gradient of DCM and methanol to afford **75** (115 mg, 43.8%). To a solution of **75** (115 mg, 0.21 mmol) in methanol, excess 4N HCl in dioxane (0.7 mL) was added. The reaction mixture was stirred at room temperature for 48 h, the boc deprotection was monitored by LCMS. The solvent was evaporated *in vacuo* and the residue was triturated with diethyl ether to afford **75** as a white solid of the dihydrochloride salt (93 mg, combined yield 37.2%). **^{1}H NMR** (600 MHz, Methanol-d_4) δ 7.45 – 7.38 (m, 2H), 7.36 (d, J = 2.1 Hz, 1H), 7.24 (d, J = 1.2 Hz, 2H), 7.16 (dd, J = 8.3, 2.1 Hz, 1H), 4.11 (t, J = 5.8 Hz, 2H), 3.98 (s, 2H), 3.92 – 3.86 (m, 2H), 2.87 (dd, J = 12.8, 2.9 Hz, 2H), 2.77 (t, J = 5.8 Hz, 2H), 2.51 (d, J = 12.0 Hz, 2H), 1.95 – 1.80 (m, 4H). **^{13}C NMR** (151 MHz, MeOD) δ 172.6, 143.4, 137.6, 136.5, 133.2, 131.7, 131.6, 131.1, 129.7, 128.6, 124.1, 124.0, 112.5, 56.1 (2C), 56.0 (2C), 55.3, 41.1, 39.6, 25.9 (2C). **UPLC/MS (Method B)**: t_R = 2.73 min, MS (ESI$^+$) 448.18 (M+H)$^+$. **HRMS (ESI) for $C_{22}H_{24}Cl_2N_3OS^+$**: Theoretical [M+H]$^+$= 448.1012 (4.5 ppm); found 448.10.32.

[0323] ***3-(2-{2,5-Diazabicyclo[2.2.1]heptan-2-yl}ethyl)-6-[(3,4-dichlorophenyl)methyl]-2,3-dihydro-1,3-benzothiazol-2-one dihydrochloride, HA221 (76)***



76, HA221

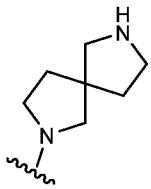
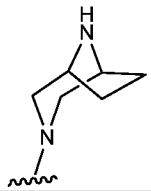
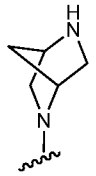
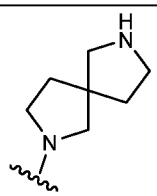
[0324] To a solution of **73** (200 mg, 0.46 mmol, 1.3 equiv.) in NMP (3 mL), (1S,4S)-(−)-2-Boc-2,5-diazabicyclo[2.2.1]heptane (70 mg, 0.35 mmol, 1 equiv.), and potassium carbonate (197.6 mg, 1.43 mmol, 4 equiv.) were added. The reaction was heated at 45 °C for 46 h. After cooling, the reaction mixture was poured onto water, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with brine, dried with Na_2SO_4, filtered, and the solvent was evaporated *in vacuo*. The crude compound was purified by silica gel chromatography using a gradient of hexane and ethyl acetate to afford **76** (74 mg, 38.8%). To a solution of **76** (74 mg, 0.138 mmol) in methanol, excess 4N HCl in dioxane (0.7 mL) was added. The reaction mixture was stirred at room temperature overnight, the boc deprotection was

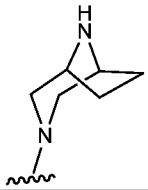
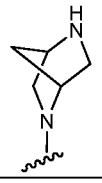
monitored by LCMS. The solvent was evaporated in *vacuo* and the residue was triturated with diethyl ether to afford **76** as a white solid of the dihydrochloride salt (67 mg, combined yield 37%). **^{1}H NMR** (600 MHz, Methanol-d_4) δ 7.47 (d, J = 1.6 Hz, 1H), 7.42 (d, J = 8.3 Hz, 1H), 7.38 – 7.34 (m, 2H), 7.29 (dd, J = 8.3, 1.8 Hz, 1H), 7.16 (dd, J = 8.3, 2.1 Hz, 1H), 4.79 – 4.74 (m, 1H), 4.60 – 4.56 (m, 1H), 4.48 – 4.36 (m, 2H), 4.00 (s, 2H), 3.86 – 3.52 (m, 6H), 2.60 – 2.51 (m, 1H), 2.26 (d, J = 12.9 Hz, 1H). **^{13}C NMR** (151 MHz, MeOD) δ 173.0, 143.4, 137.9, 136.1, 133.2, 131.7, 131.6, 131.1, 129.7, 128.8, 124.3, 124.2, 112.3, 64.2, 58.2, 57.3, 57.2 (2C), 41.1, 39.6, 34.1 (CH_2 confirmed by HSQC). **HRMS (ESI) for $C_{21}H_{22}Cl_2N_3OS^+$**: Theoretical $[M+H]^+$= 434.0855 (3.5 ppm); found 434.0870.

Metabolic Stability

[0325] Metabolic stability studies on compounds of Formula (III) were carried out as described above.

[0326] Table 3A: *In vitro* metabolic stability

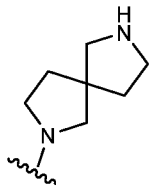
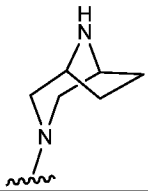
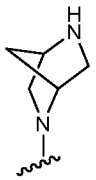
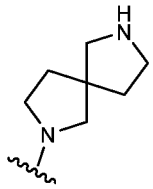
Comp.	Compound code	R^4	X^4	$t_{½}$ (min)	Cl int (µl/min/mg)
69	**HA183**		CO	**>30**	**9.8**
70	**HA182**		CO	**>30**	**1.2**
71	**HA228**		CO	**>30**	**0.9**
74	**HA186**		CH_2	**27.4**	**25.3**

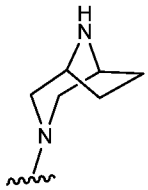
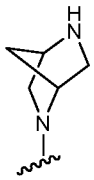
Comp.	Compound code	R^4	X^4	$t_{½}$ (min)	Cl int (µl/min/mg)
75	**HA163**		CH_2	**>30**	**1.1**
76	**HA221**		CH_2	**>30**	**1.7**

Binding Affinity

[0327] Binding affinity studies on compounds of Formula (III) were carried out as described above.

[0328] Table 3B: *In vitro* binding affinity

#	Comp code	R	X	*K*i (nM ± SD)	
				S1R	S2R
CM304		-	-	3.45 ± 0.70	595.27 ± 144.75
69	HA183		CO	169.65 ± 9.85	107.03 ± 35.12
70	HA182		CO	ND	227.37 ± 10.91
71	HA228		CO	ND	ND
74	HA186		CH_2	129.84 ±15.83	247.78 ± 50.24

#	Comp code	R	X	*K*i (nM ± SD)	
				S1R	S2R
75	HA163		CH_2	416.0 ± 97.78	702.67 ± 131.58
76	HA221		CH_2	323.9 ±110.21	300.44 ± 51.73

EQUIVALENTS AND SCOPE

[0329] In the claims articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The present disclosure includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The present disclosure includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[0330] Furthermore, the present disclosure encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, e.g., in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should it be understood that, in general, where the present disclosure, or aspects of the present disclosure, is/are referred to as comprising particular elements and/or features, certain embodiments of the present disclosure or aspects of the present disclosure consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth in haec verba herein. It is also noted that the terms "comprising" and "containing" are intended to be open and permits the

inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the present disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

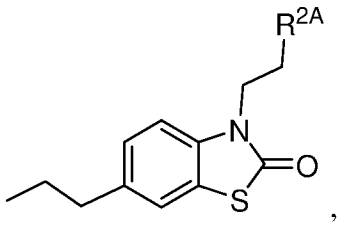
[0331] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present disclosure that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the present disclosure can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

[0332] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present disclosure, as defined in the following claims.

CLAIMS

What is claimed is:

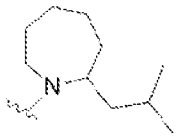
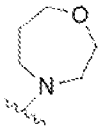
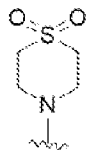
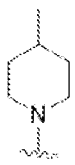
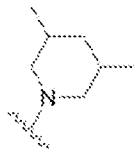
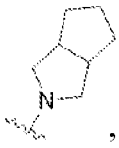
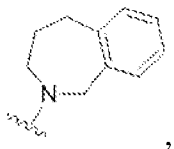
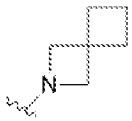
1. A compound of Formula (I):

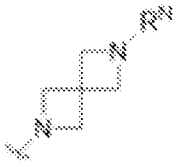
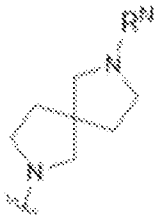
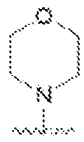
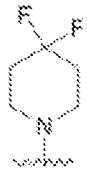


(I)

or pharmaceutically acceptable salt thereof, wherein:

R^{2A} is selected from the group consisting of:

substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted

 , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , substituted or unsubstituted  , and substituted or unsubstituted  ;

wherein the substituted R^{2A} is substituted with one or more substituents independently selected from halo, C_{1-6} alkyl, -OH, -O(C_{1-6} alkyl), -NH_2, and -NMe_2;

R^N is H, C_{1-6} alkyl, or a nitrogen protecting group; and

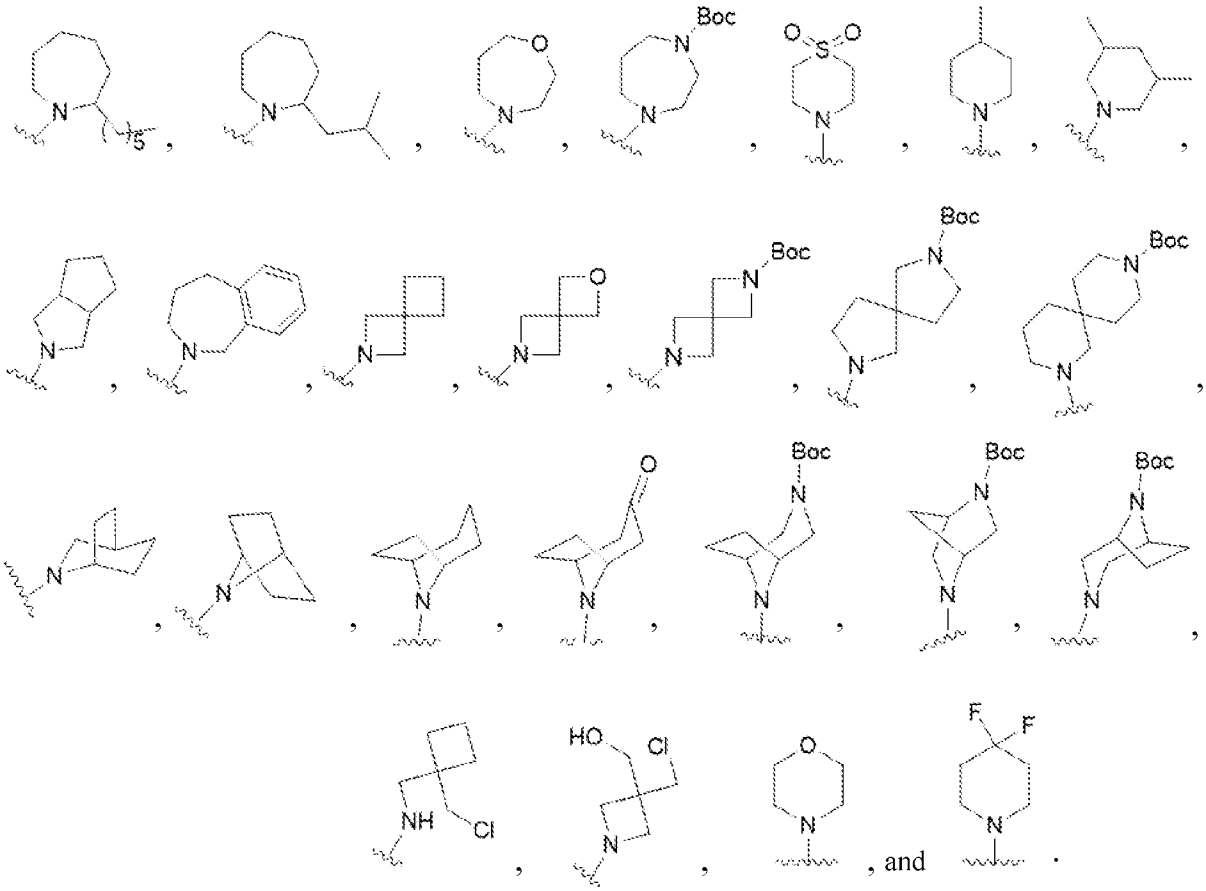
m is 1, 2, 3, 4, 5, or 6.

2. The compound of claim 1, or pharmaceutically acceptable salt thereof, wherein R^N is H, methyl, or Boc.

3. The compound of claim 1 or 2, or pharmaceutically acceptable salt thereof, wherein m is 4, 5, or 6.

4. The compound of any one of claims 1-3, or pharmaceutically acceptable salt thereof, wherein m is 5.

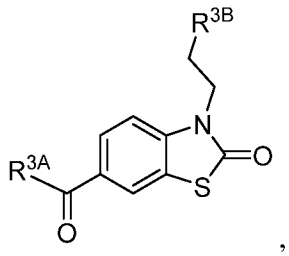
5. The compound of any one of claims 1-4, or pharmaceutically acceptable salt thereof, wherein R^{2A} is selected from the group consisting of:



6. The compound of any one of claims 1-5, or pharmaceutically acceptable salt thereof, wherein R^{2A} is unsubstituted.

7. The compound of any one of claims 1-6, or pharmaceutically acceptable salt thereof, wherein R^{2A} is substituted with halo or C_{1-6} alkyl.

8. A compound of Formula (II):



(II)

or pharmaceutically acceptable salt thereof, wherein:

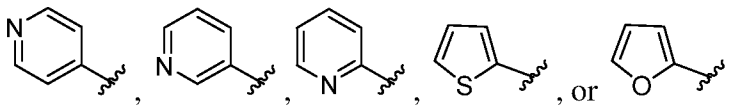
R^{3A} is selected from the group consisting of unsubstituted or substituted pyridinyl, unsubstituted or substituted furanyl, and unsubstituted or substituted thiopheneyl; and

R^{3B} is selected from the group consisting of unsubstituted or substituted piperidinyl, unsubstituted or substituted morpholinyl, unsubstituted or substituted azepanyl, unsubstituted or substituted oxazepanyl, and unsubstituted or substituted 3,8-diazabicyclo[3.2.1]octanyl;

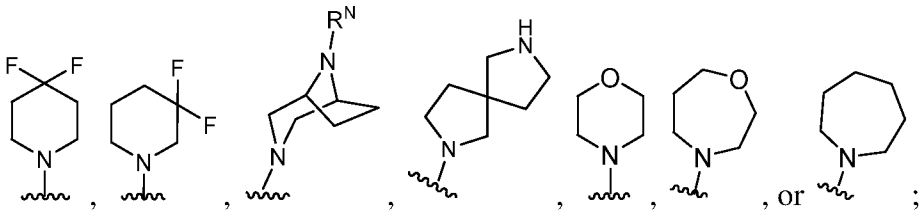
wherein the substituted R^{3A} and substituted R^{3B} are independently substituted with one or more substituents independently selected from halo, C_{1-6} alkyl, -OH, -O(C_{1-6} alkyl), $-NH_2$, and $-NMe_2$; and

wherein substituted R^{3B} is further optionally substituted with R^N, wherein R^N is H, C_{1-6} alkyl, or a nitrogen protecting group.

9. The compound of claim 8, or pharmaceutically acceptable salt thereof, wherein R^{3A} is



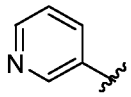
10. The compound of any one of claim 8 or 9, or pharmaceutically acceptable salt thereof,

wherein R^{3B} is  ;

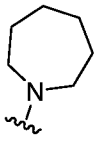
wherein R^N is H, C_{1-6} alkyl, or a nitrogen protecting group.

11. The compound of claim 10, or pharmaceutically acceptable salt thereof, wherein R^N is H, methyl, or Boc.

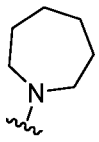
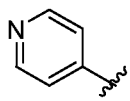
12. The compound of any one of claims 8-11, or pharmaceutically acceptable salt thereof,

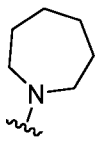
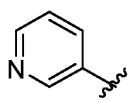
wherein R^{3A} is  .

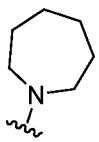
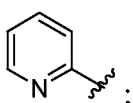
13. The compound of any one of claims 8-11, or pharmaceutically acceptable salt thereof,

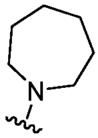
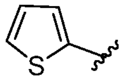
wherein R^{3B} is  .

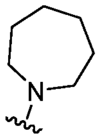
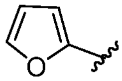
14. The compound of claim 8, or pharmaceutically acceptable salt thereof, wherein:

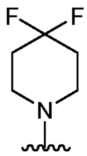
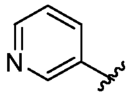
R^{3B} is  and R^{3A} is  ;

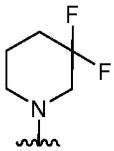
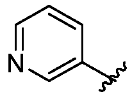
R^{3B} is  and R^{3A} is  ;

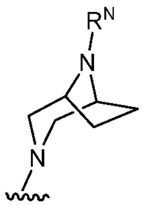
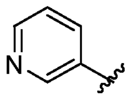
R^{3B} is  and R^{3A} is  ;

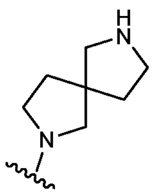
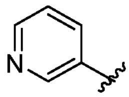
R^{3B} is  and R^{3A} is  ;

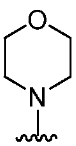
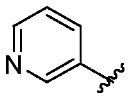
R^{3B} is  and R^{3A} is  ;

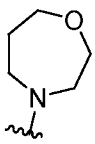
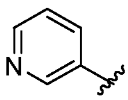
R^{3B} is  and R^{3A} is  ;

R^{3B} is  and R^{3A} is  ;

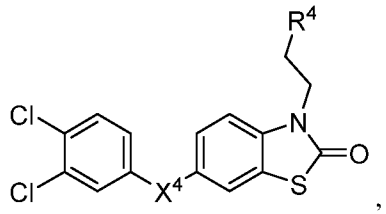
R^{3B} is  and R^{3A} is  ;

R^{3B} is  and R^{3A} is  ;

R^{3B} is  and R^{3A} is  ; or

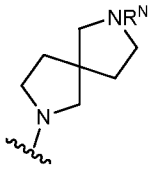
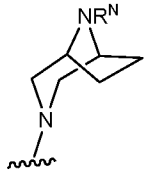
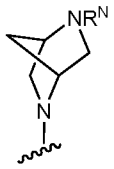
R^{3B} is  and R^{3A} is  .

15. A compound of Formula (III):



(III)

or pharmaceutically acceptable salt thereof, wherein:

R^4 is unsubstituted or substituted  , unsubstituted or substituted  , or unsubstituted or substituted  ;

wherein the substituted R^4 is substituted with one or more substituents independently selected from halo, $C_{1\text{-}6}$ alkyl, -OH, -O($C_{1\text{-}6}$ alkyl), -NH_2, and -NMe_2;

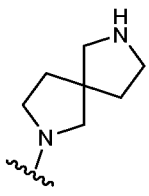
R^N is H, $C_{1\text{-}6}$ alkyl, or a nitrogen protecting group; and

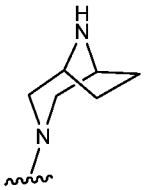
X^4 is -CH_2- or -C(=O)-.

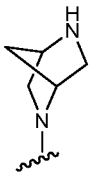
16. The compound of claim 15, or pharmaceutically acceptable salt thereof, wherein R^4 is unsubstituted.

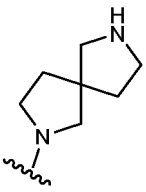
17. The compound of claim 15 or 16, or pharmaceutically acceptable salt thereof, wherein R^N is H, methyl, or Boc.

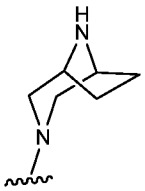
18. The compound of any one of claims 15-17, or pharmaceutically acceptable salt thereof, wherein:

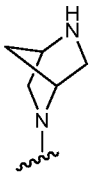
R^4 is  and X^4 is -CH_2-;

R^4 is  and X^4 is -CH_2-;

R^4 is  and X^4 is -CH_2-;

R^4 is  and X^4 is -C(=O)-;

R^4 is  and X^4 is -C(=O)-; or

R^4 is  and X^4 is -C(=O)-.

19. The compound of any one of claims 1-18, or pharmaceutically acceptable salt thereof, wherein the compound is sigma-receptor antagonist.

20. The compound of any one of claims 1-18, or pharmaceutically acceptable salt thereof, wherein the compound is metabolically stable.

21. A composition comprising the compound of any one of claims 1-20, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

22. A method of treating or preventing a disease or disorder associated with one or more sigma receptors comprising administering to a subject a therapeutically effective amount of the

compound of any one of claims 1-20, or pharmaceutically acceptable salt thereof, or composition of claim 21.

23. The method of claim 22, wherein the disease or disorder is a neurological disease, a proliferative disease, a painful condition, or a psychiatric disorder.

24. The method of claim 22 or 23, wherein the disease or disorder is pain, a neurodegenerative disorder (*e.g.*, Alzheimer's disease, Parkinson's disease), substance addiction, cancer, depression, schizophrenia, anxiety, stroke, obsessive compulsive disorder, or multiple sclerosis.

25. A method of treating or preventing substance intake by a subject comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1-20, or pharmaceutically acceptable salt thereof, or composition of claim 21.

26. A method of treating or preventing substance use disorder in a subject comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1-20, or pharmaceutically acceptable salt thereof, or composition of claim 21.

27. A method of treating the symptoms of substance use disorder in a subject comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1-20, or pharmaceutically acceptable salt thereof, or composition of claim 21.

28. A method of treating or preventing substance addiction in a subject comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1-20, or pharmaceutically acceptable salt thereof, or composition of claim 21.

29. A method of treating the symptoms of substance addiction in a subject comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1-20, or pharmaceutically acceptable salt thereof, or composition of claim 21.

30. A method of treating or preventing neurotoxic effects resulting from substance use disorder, substance addiction, and/or substance intake by a subject comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1-20, or pharmaceutically acceptable salt thereof, or composition of claim 21.

31. The method of any one of claims 25-30, wherein the substance is methamphetamine.

32. The method of any one of claims 25-30, wherein the substance is cocaine.

33. A kit comprising:

the compound of any one of claims 1-20, or pharmaceutically acceptable salt thereof, or composition of claim 21; and

and instructions for administering the compound, or pharmaceutically acceptable salt thereof, or composition to a subject.

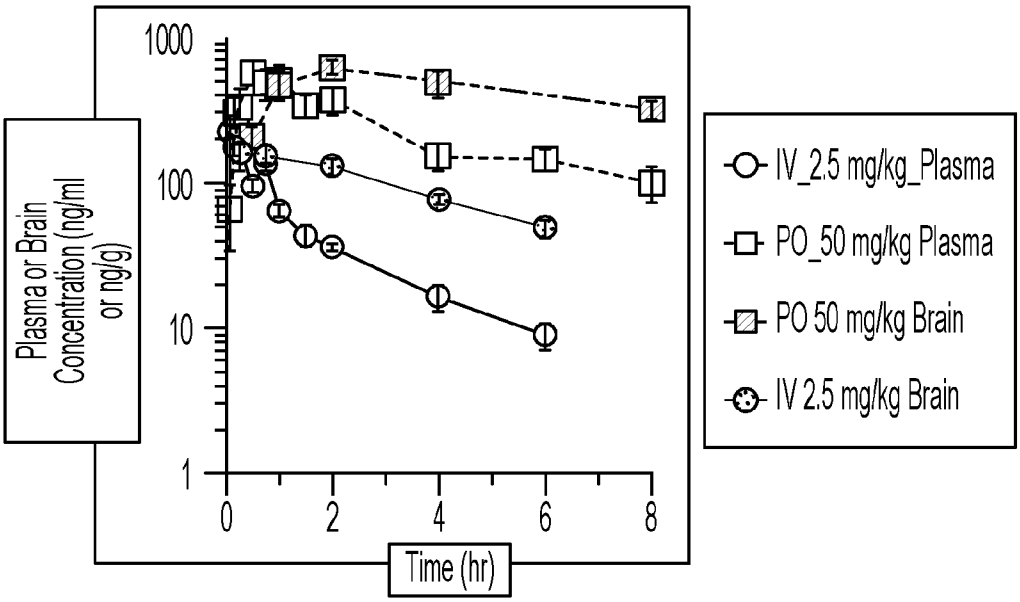

1000
100
10
1
0
2
4
6
8
Plasma or Brain Concentration (ng/ml or ng/g)
Time (hr)
IV_2.5 mg/kg_Plasma
PO_50 mg/kg Plasma
PO 50 mg/kg Brain
IV 2.5 mg/kg Brain

FIG. 1A

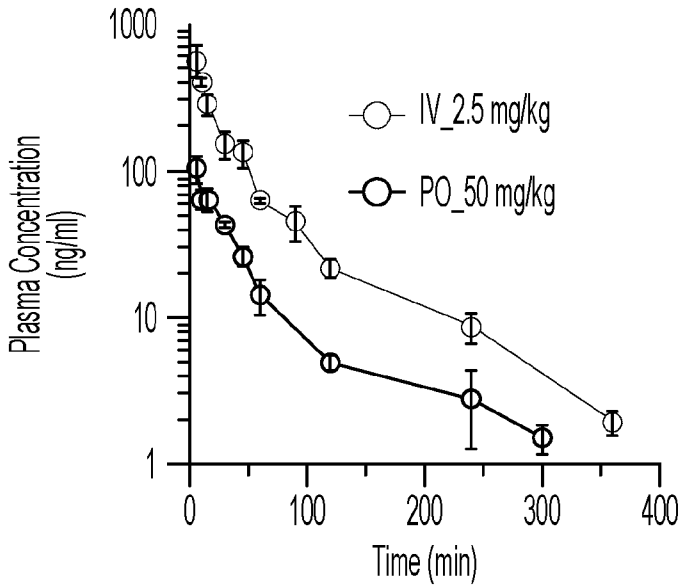

1000
100
10
1
0
100
200
300
400
Plasma Concentration (ng/ml)
Time (min)
IV_2.5 mg/kg
PO_50 mg/kg

FIG. 1B